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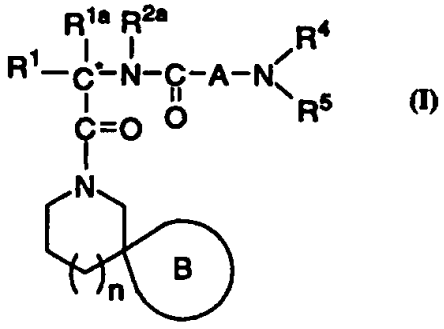
(54) Title: 3-SPIROLACTAM, 3-SPIROAMINO, 3-SPIROLACTONE AND 3-SPIROBENZOPYRAN PIPERIDINES AND PYRROLIDINES PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

The present invention is directed to certain novel compounds of general structural formula (I) wherein R^1, R^{1a}, R^{2a}, R^4, R^5, A, and B are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing these compounds as the active ingredient thereof are also disclosed.



(I)

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TITLE OF THE INVENTION

3-SPIROLACTAM, 3-SPIROAMINO, 3-SPIROLACTONE AND 3-SPIROBENZOPYRAN PIPERIDINES AND PYRROLIDINES PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any

risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray. Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone secretagogues with a benzolactam structure are disclosed in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. Other growth hormone secretagogues are disclosed e.g., in PCT Patent Publications WO 94/13696, WO 94/19367, and WO 95/09633. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

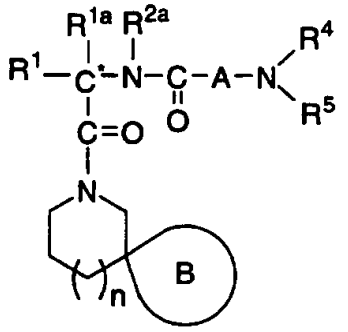
SUMMARY OF THE INVENTION

The instant invention is directed to certain 3-spirolactam, 3-spiroamino, 3-spirolactone, 3-spirobenzopyran and 3-spirobenzothiapyran piperidine and pyrrolidine compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the compounds for the use of treating humans and animals so as to increase the level of growth hormone

secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel compounds of the instant invention are described by structural Formula I:



Formula I

wherein:

R^1 is selected from the group consisting of:
C_1-C_{10} alkyl, aryl, aryl (C_1-C_6 alkyl),
(C_3-C_7 cycloalkyl)(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
aryl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and
(C_3-C_7 cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
where K is -O-, -S(O)$_m$-, -N(R^2)C(O)-, -C(O)N(R^2)-, -OC(O)-, -C(O)O-, -CR^2=CR^2-, or -C≡C-, where R^2 and alkyl may be further substituted by 1 to 9 halogen, S(O)$_m$$R^{2a}$, 1 to 3 of O$R^{2a}$ or C(O)OR^{2a}, and aryl is selected from: phenyl, naphthyl, quinolinyl, isoquinolinyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where the aryl is unsubstituted or substituted with a substitutent selected from: 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR^2, methylenedioxy, -S(O)$_m$$R^2$, 1 to 2 of -$CF_3$, -$OCF_3$, nitro, -N($R^2$)C(O)($R^2$), -C(O)O$R^2$, -C(O)N($R^2$)($R^2$), -1H-tetrazol-5-yl, -$SO_2$N($R^2$)($R^2$), -N($R^2$)$SO_2$ phenyl, or -N(R^2)$SO_2$$R^2$;

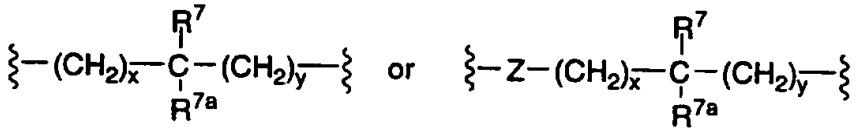
R^{1a} is select d from hydrogen and C_1-C_6 alkyl;

R^2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they optionally are joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

R^{2a} is selected from hydrogen and C_1-C_6 alkyl;

R^4 and R^5 are independently hydrogen, unsubsubstituted C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituent is selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenyloxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl), or R^4 and R^5 may be taken together to form $-(CH_2)_d$-$L_a(CH_2)_e$- where L_a is $-C(R^2)_2$-, -O-, $-S(O)_m$- or $-N(R^2)$-, d and e are independently 1 to 3 and R^2 is as defined above;

A is:



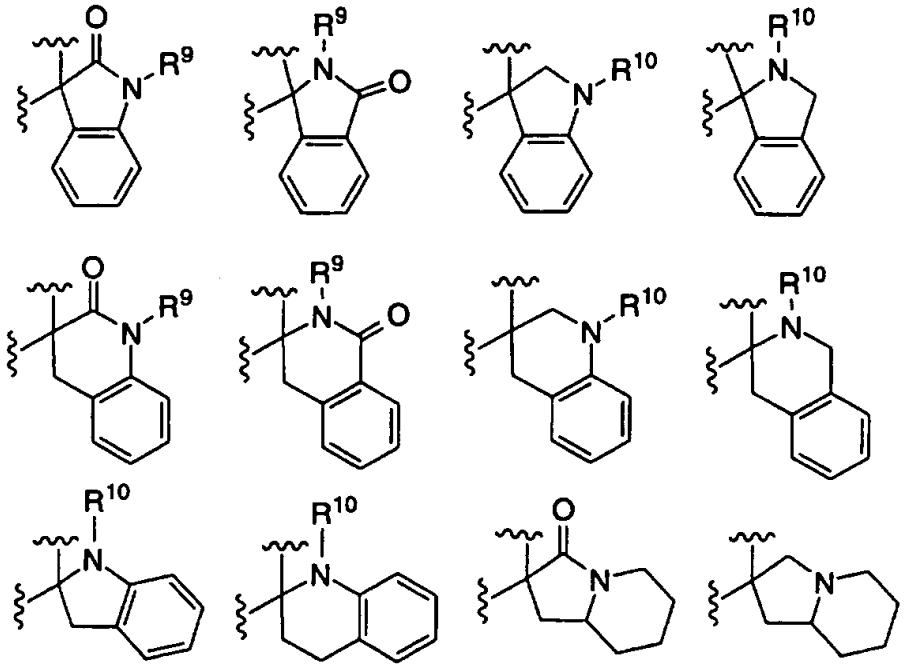
where x and y are independently 0, 1, 2 or 3;

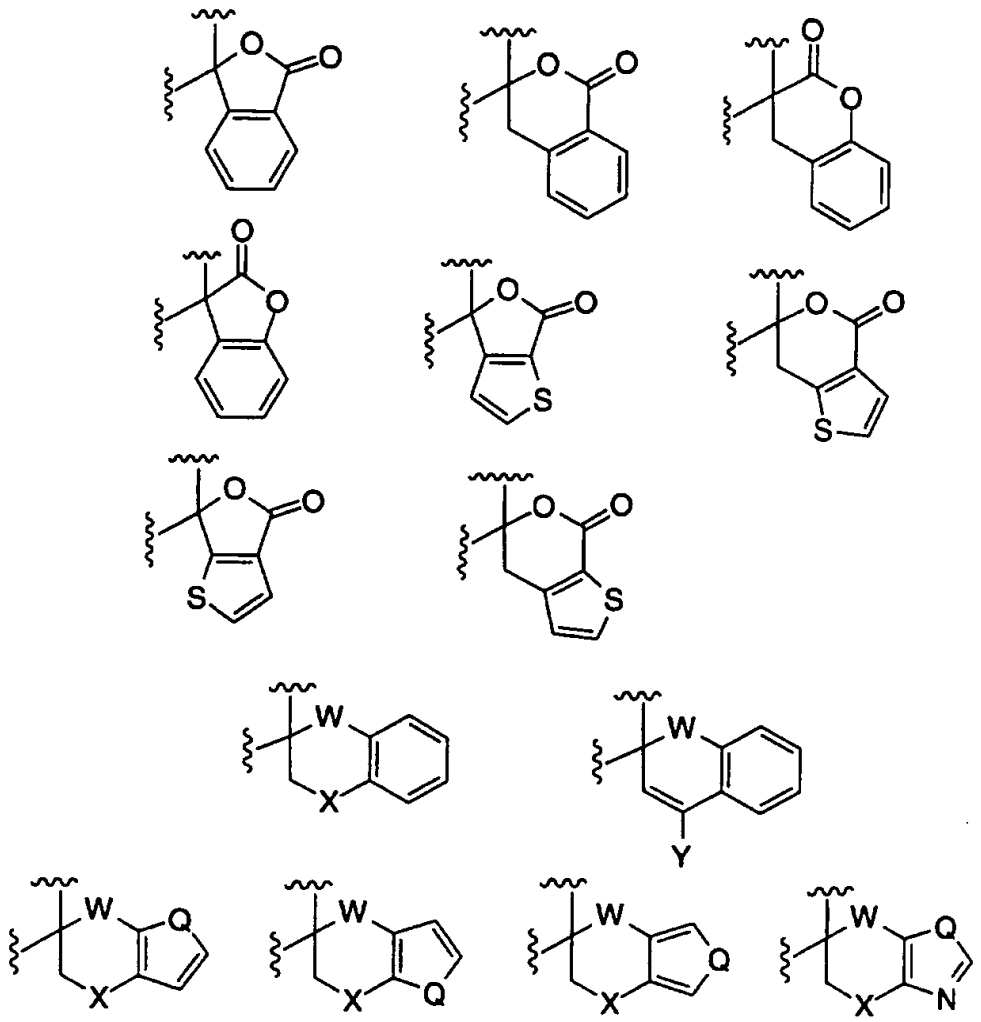
Z is $-N(R^{6a})$- or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl and the C_1-C_6 alkyl is optionally joined to R^4 or R^5 to form a five, six or seven membered ring;

R^7 and R^{7a} are independently hydrogen, unsubstituted C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3-C_7 cycloalkyl, $-N(R^2)(R^2)$, and $-C(O)N(R^2)(R^2)$; or R^7 and R^{7a} independently may be joined to one or both of R^4 and R^5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^7 or R^{7a} groups, wherein

the bridge contains 1 to 5 carbons atoms; or R^7 and R^{7a} are optionally joined to one another to form a C_3-C_7 cycloalkyl;

B is selected from the group consisting of:





where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

where W is selected from -O- and -S-,
Q is selected from -O-, -S- and -$N(R^2)$-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
m is 0, 1, or 2; and
n is 0 or 1;
and the hydroxy acid open lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration and if two carbon atoms or more they may include a double or a triple bond. Exemplary of such alkyl groups are

methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propargyl, and the like.

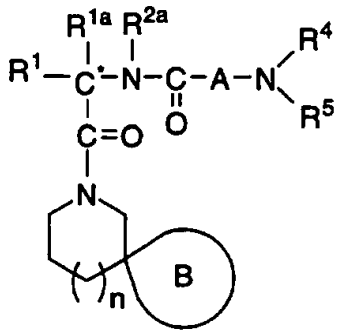
The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings including: phenyl, naphthyl, thiazolyl, thiadiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, thiopheneyl, pyrimidinyl, pyrazolyl, pyrrazinyl, quinolinyl, and isoquinolinyl, which are unsubstituted or substituted with 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -OCF_3, nitro, -$N(R^2)C(O)(R^2)$, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, -1H-tetrazol-5-yl, -$SO_2N(R^2)(R^2)$, -$N(R^2)SO_2$ phenyl, or -$N(R^2)SO_2R^2$, wherein R^2 is as defined herein.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:



Formula Ia

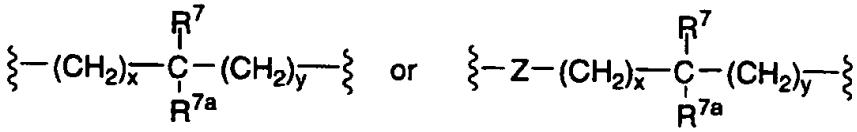
wherein:

R^1 is selected from the group consisting of:
C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl (C_1-C_4 alkyl)-, (C_1-C_4 alkyl)-K-(C_1-C_2 alkyl)-, aryl (C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, where K is -O-, -$S(O)_m$-, -OC(O)-, or -C(O)O-, and the alkyl groups may be further substituted by 1 to 7 halogen, -$S(O)_mR^2$, 1 to 3 -OR^2 or -$C(O)OR^2$, and aryl is selected from: phenyl, naphthyl, quinolinyl, isoquinolinyl, indolyl, pyridyl, benzimidazolyl, azaindolyl, benzothienyl and benzofuranyl and where the aryl is unsubstituted or substituted with a substitutent selected from: 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, and -$C(O)OR^2$;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_4-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_4 alkyl;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituent is selected from: 1 to 5 halo, 1 to 3 hydroxyl, -S(O)m (C_1-C_6 alkyl) and phenyl;

A is:

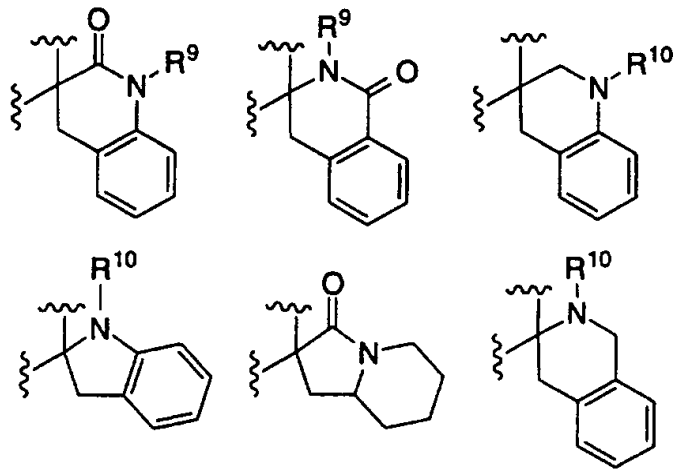


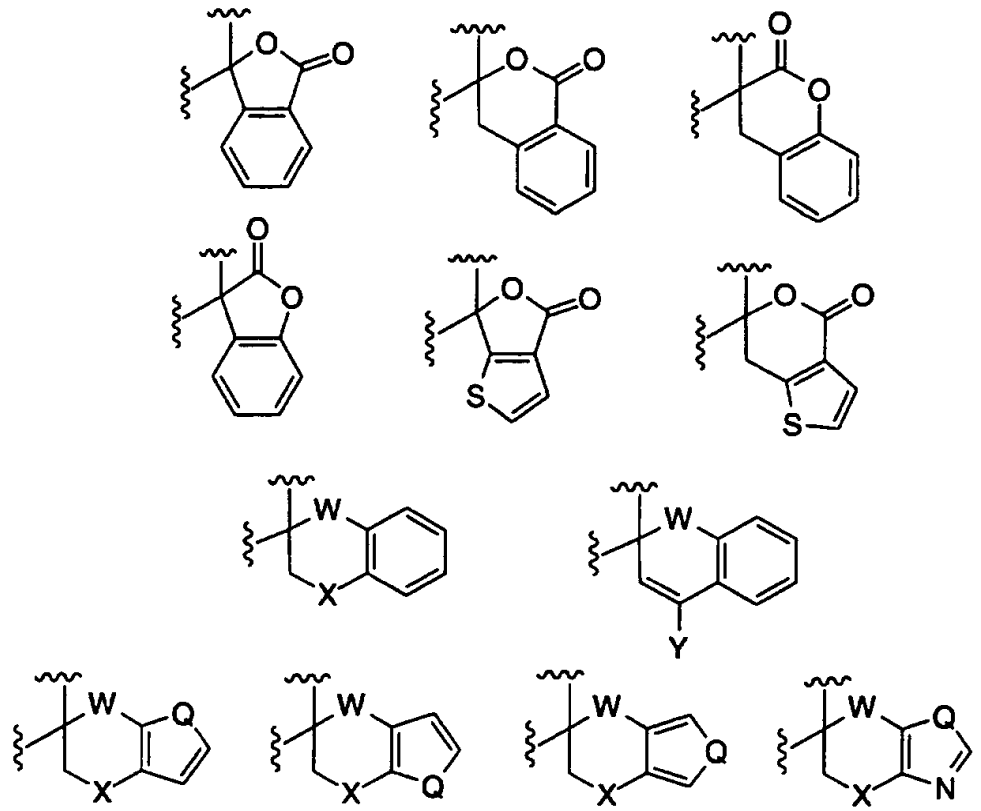
where x and y are independently 0, 1 or 2;

Z is -NR6a- or -O-, where R6a is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R4 or R5 to form a six or seven membered ring;

R7 and R7a are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, OR^2, $S(O)mR^2$, $C(O)OR^2$, C_5-C_7 cycloalkyl, $-N(R^2)(R^2)$, and $-C(O)N(R^2)(R^2)$; or R7 and R7a can independently be joined to one of R4 or R5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of R7 or R7a groups to form 5 or 6 membered rings; or R7 and R7a can be joined to one another to form a C_3 cycloalkyl;

B is selected from the group consisting of:





where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

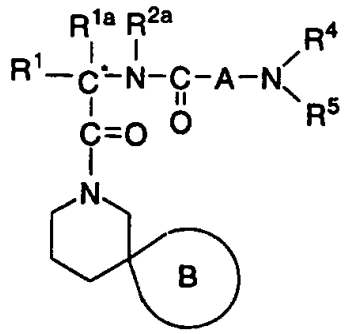
R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl,

where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, and $-C(O)N(R^2)(R^2)$;

where W is selected from -O- and -S-,
Q is selected from -O-, -S- and $-N(R^2)-$,
X is selected from the group consisting of: $-CH_2-$, -C(O)-, $-CH(OR^2)-$, $CH-O-C(O)R^2$, $CH-O-C(O)N(R^2)(R^2)$, $CH-C(O)OR^2$ and $CH-C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, $-C(O)OR^2$ and $-C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, and $-C(O)N(R^2)(R^2)$;
m is 0, 1, or 2; and
n is 0 or 1;

and the hydroxy acid open lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

More preferred compounds of the instant invention include those of Formula Ib:



Formula 1b

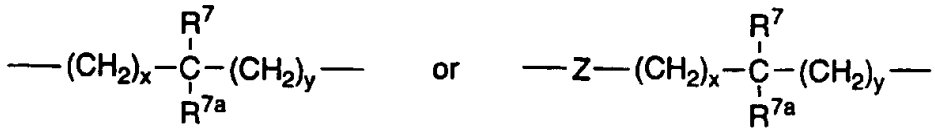
wherein:

R^1 is selected from the group consisting of: C_1-C_{10} alkyl, aryl (C_1-C_3 alkyl)-, (C_3-C_7 cycloalkyl)(C_1-C_3 alkyl)-, and aryl (C_0-C_1 alkyl)-K-(C_1-C_2 alkyl)-, where K is O or $S(O)_m$ and the aryl is selected from: phenyl, pyridyl, naphthyl, quinolinyl, isoquinolinyl, indolyl, azaindolyl, benzothienyl, and benzimidazolyl and where the aryl is unsubstituted or substituted with a substitutent selected from: 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or $C(O)OR^2$;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a} where R^{3a} is hydrogen, or C_1-C_3 alkyl;

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, or substituted C_1-C_3 alkyl where the substituent is 1 to 2 hydroxyl;

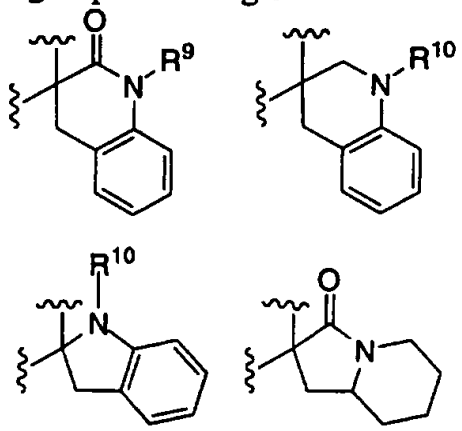
A is:

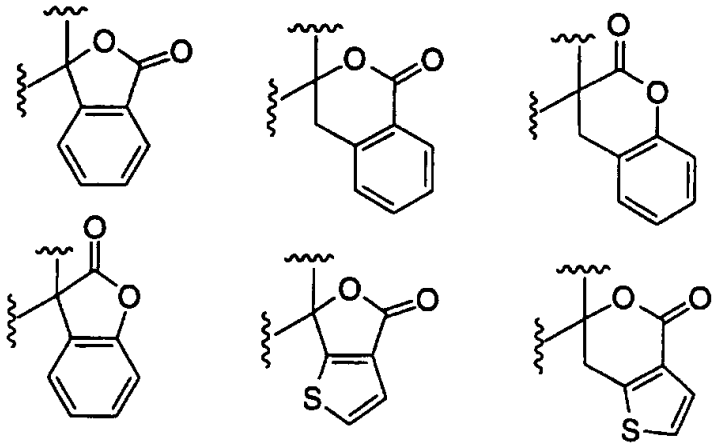


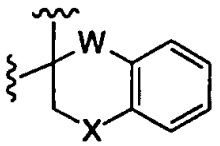
where x and y are independantly 0, 1, or 2;
Z is -N(R^{6a})- or -O-, where R^{6a} is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R^4 or R^5 to form a six or seven membered ring;

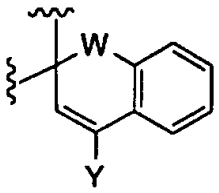
R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, phenyl, substituted C_1-C_6 alkyl where the substitutent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^2, and -$S(O)_mR^2$, or R^7 and R^{7a} can independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 or R^{7a} can be joined to one another to form a C_3-C_6 cycloalkyl;

B is selected from the group consisting of:









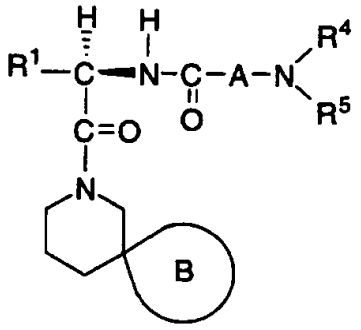
where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

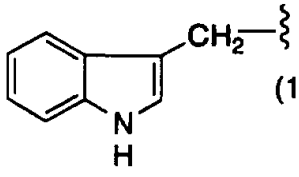
m is 0, 1, or 2; and
and the hydroxy acid open lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

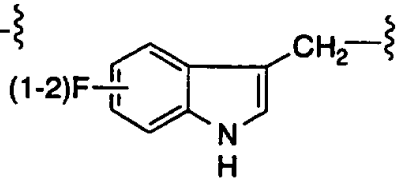
Still more preferred compounds of the instant invention include those of Formula Ic:

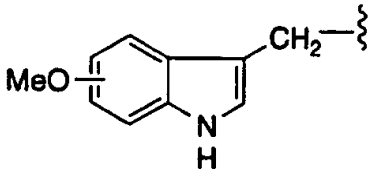


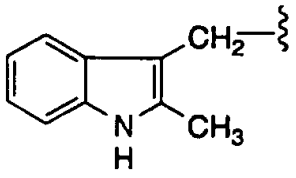
Formula Ic

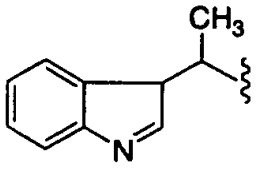
wherein:
R1 is selected from the group consisting of:

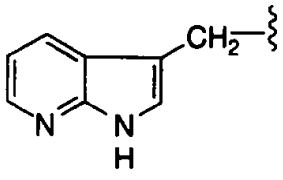


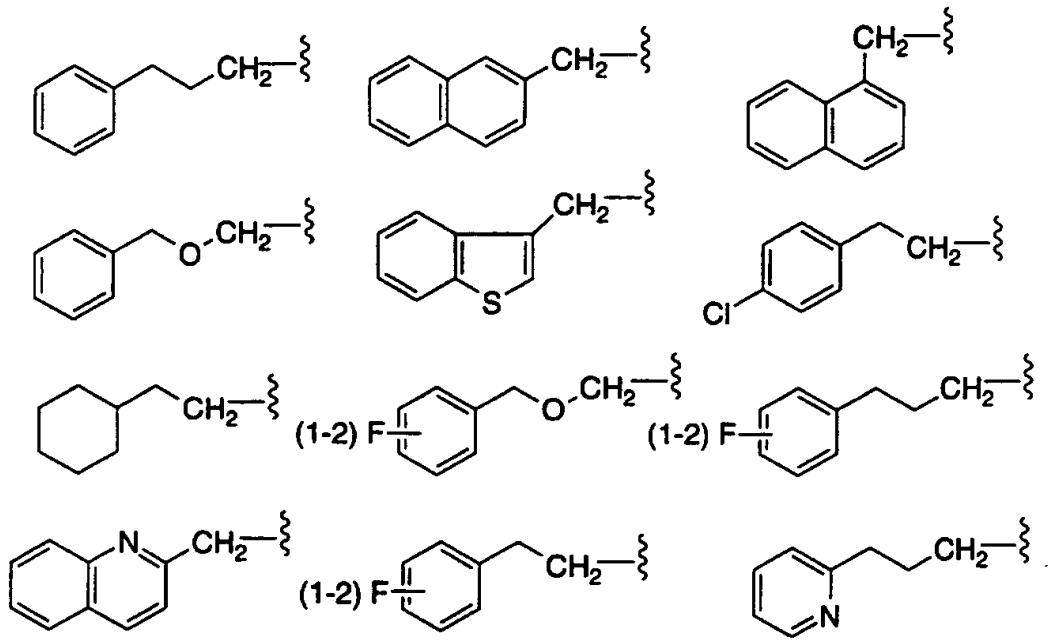








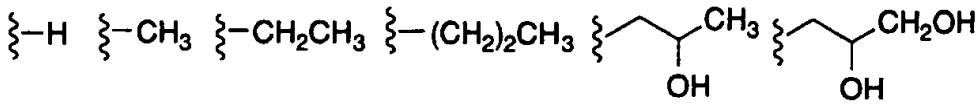




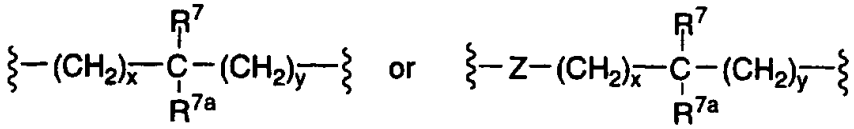
or their regioisomers where not specified;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a} where R^{3a} is hydrogen, or C_1-C_2 alkyl;

R^4 and R^5 are independently selected from the group consisting of:



A is:

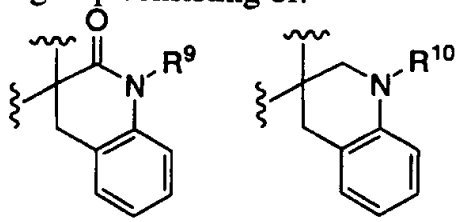


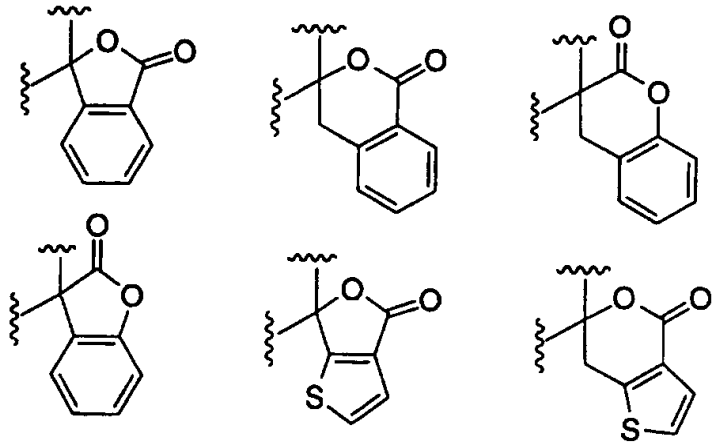
where x and y are independently 0, 1, or 2;

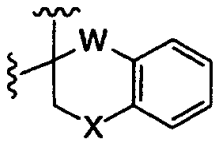
Z is -(NR6a)- or -O-, where R6a is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R4 or R5 to form a six membered ring;

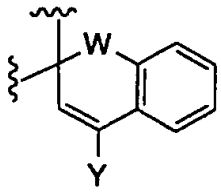
R7 and R7a are independently hydrogen, unsubstituted C_1-C_6 alkyl or substituted C_1-C_6 alkyl wherein the substituent is selected from: phenyl, naphthyl and indolyl; or R7 and R7a independently may be joined to one of R4 or R5 to form an alkylene bridge between the terminal nitrogen and the alkyl portions of R7 or R7a to form a 5 or 6 membered ring;

B is selected from the group consisting of:









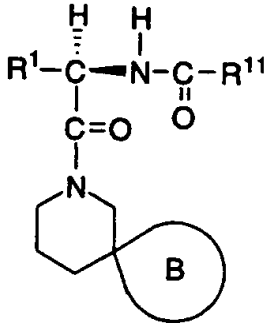
where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, thienyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
m is 0, 1 or 2;

and pharmaceutically acceptable salts and individual diasteromers thereof.

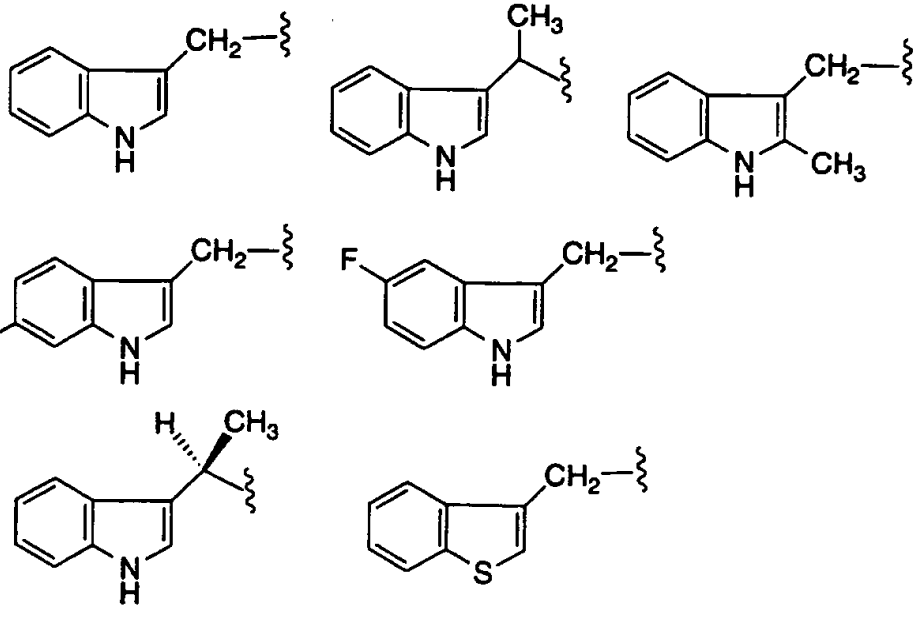
The most preferred compounds of the instant invention include those of Formula Id:



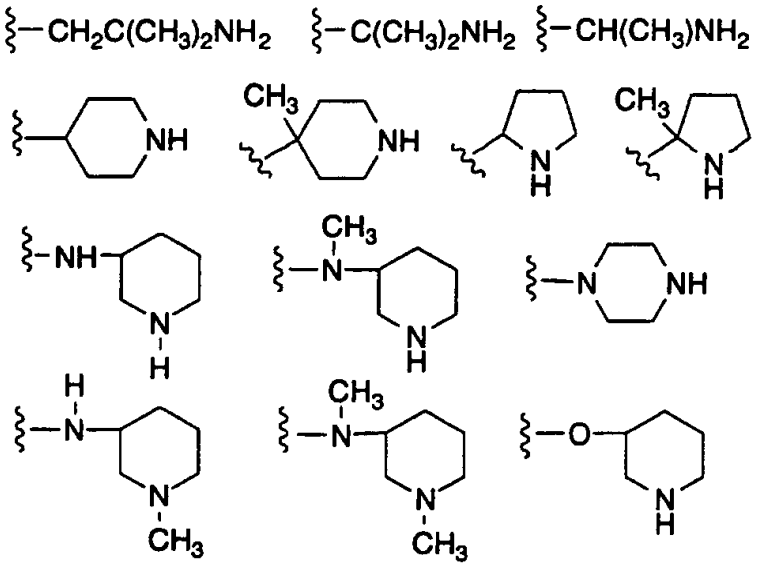
Formula Id

wherein:

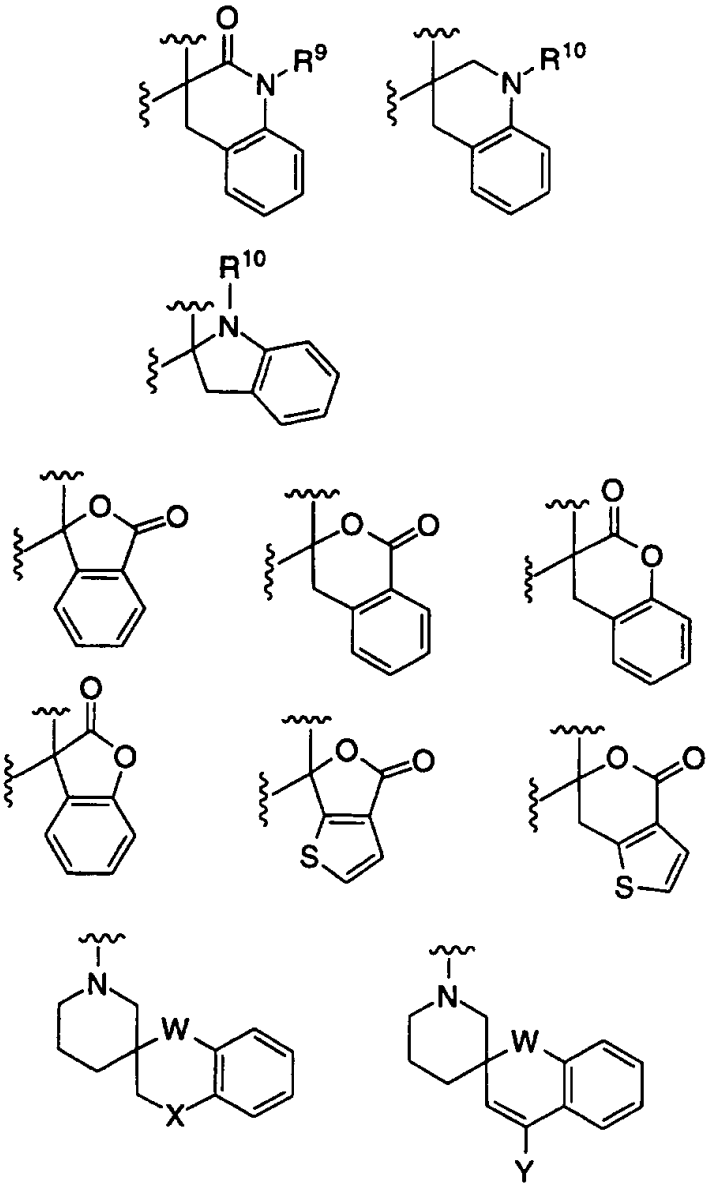
R^1 is selected from the group consisting of:



R11 is selected from the group consisting of:



B is selected from the group consisting of:



where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

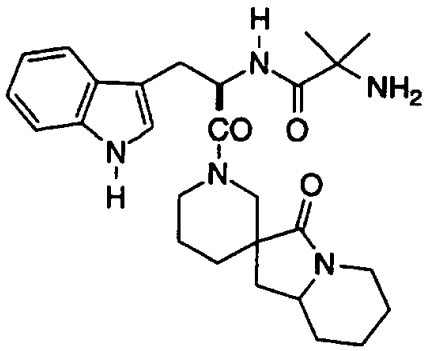
R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

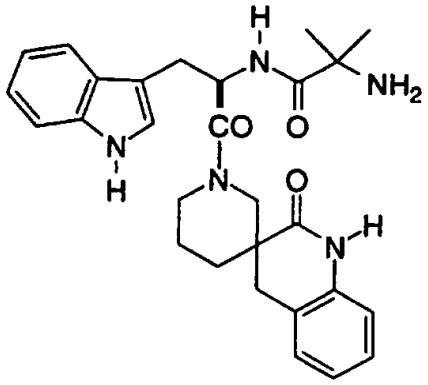
R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, and indolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

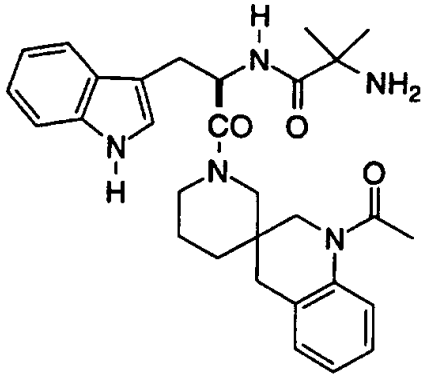
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

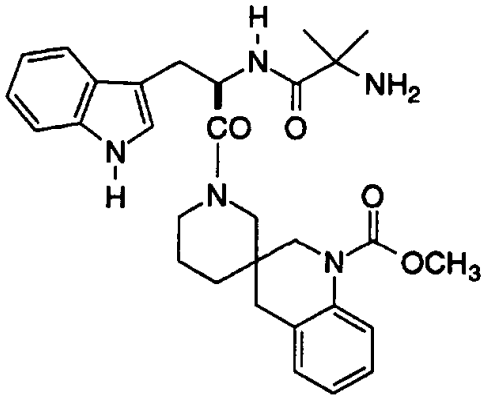
and pharmaceutically acceptable salts and individual diasteromers thereof.

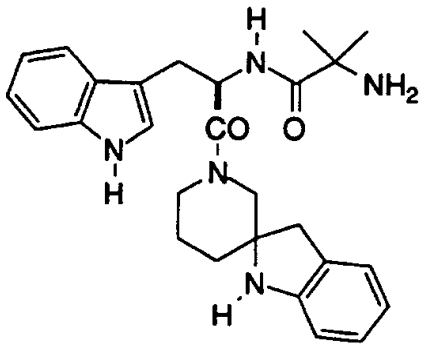
Specific compounds within the scope of the instant invention include:

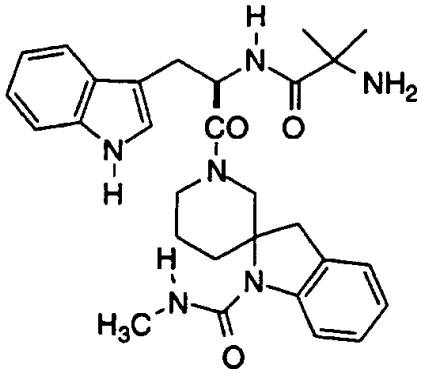


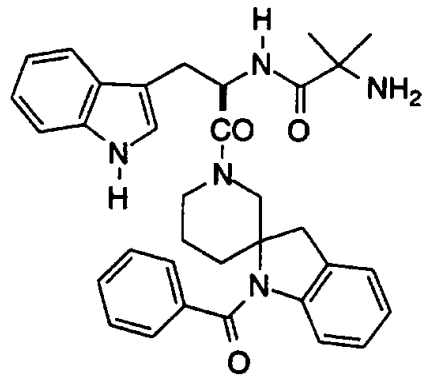


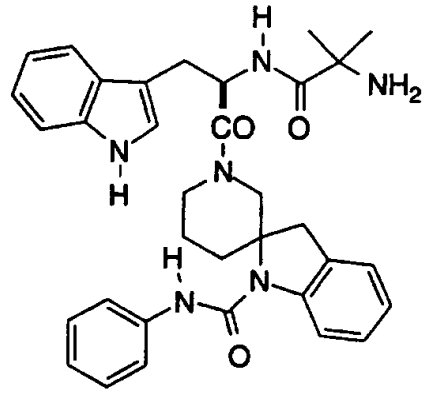


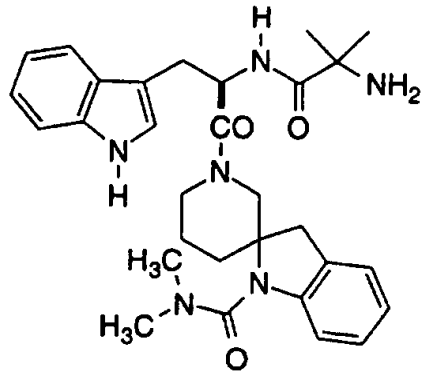


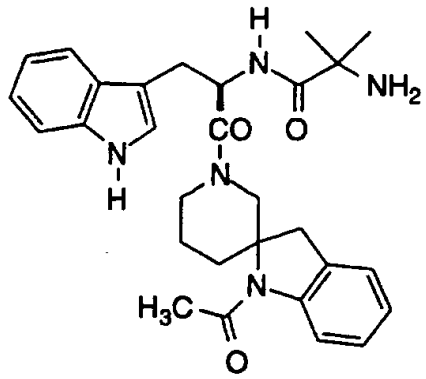


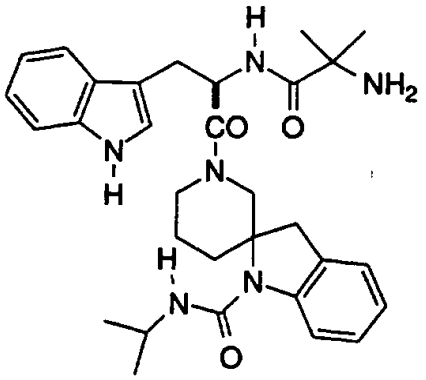


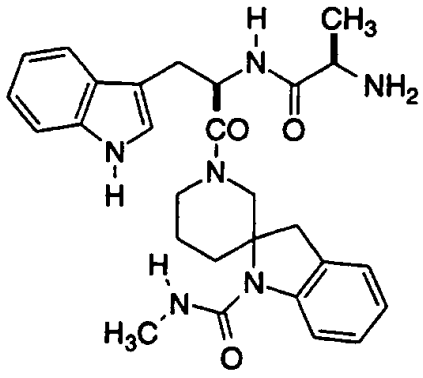


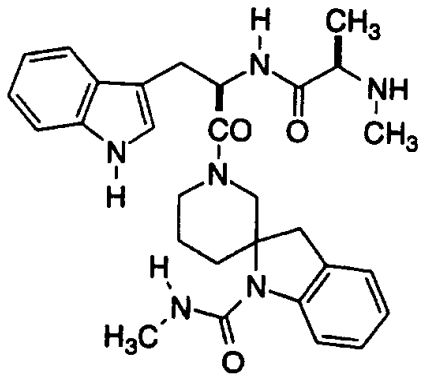


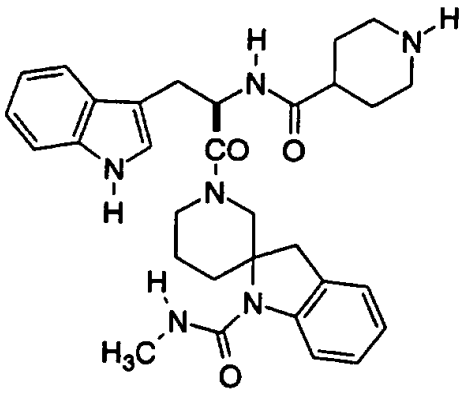


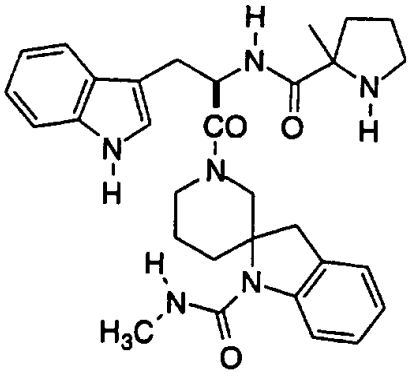


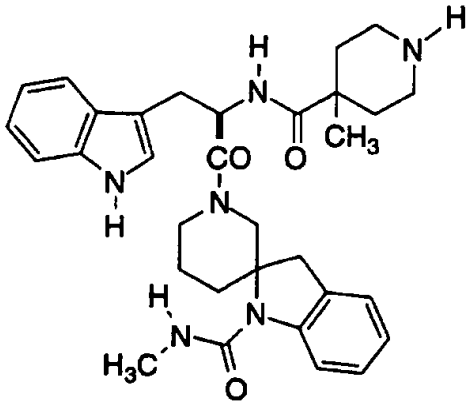


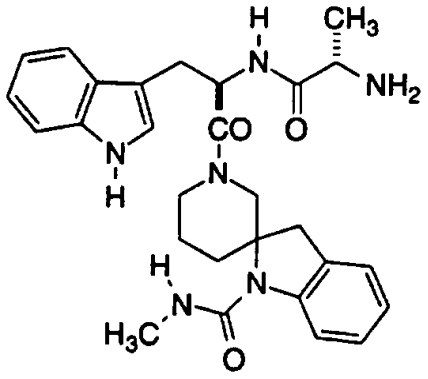


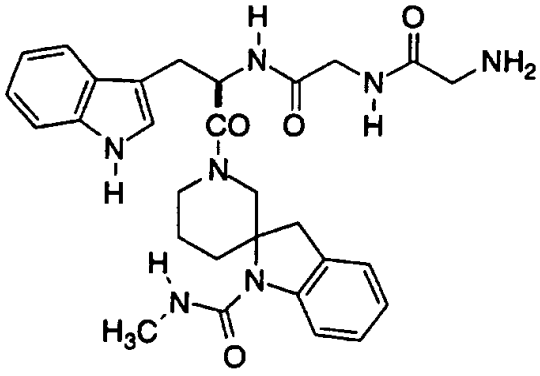


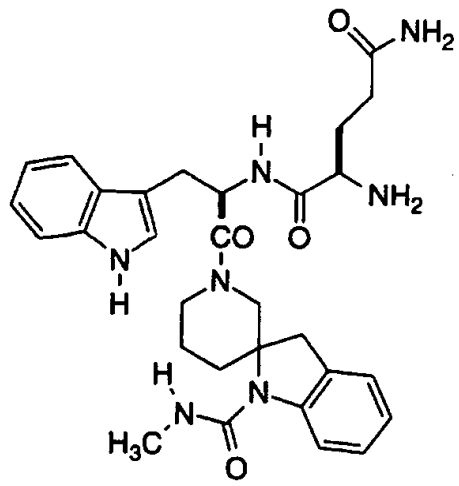


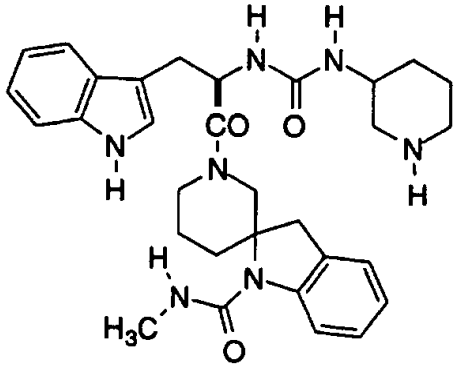


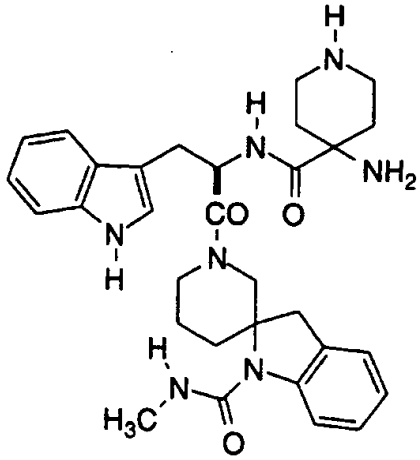


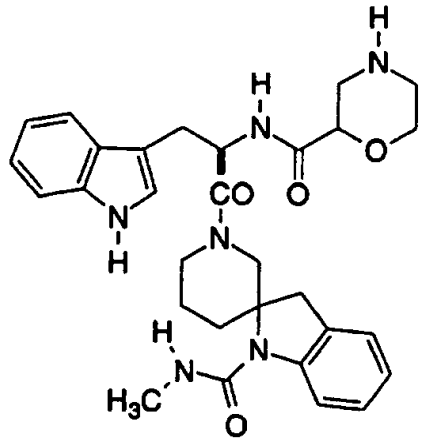


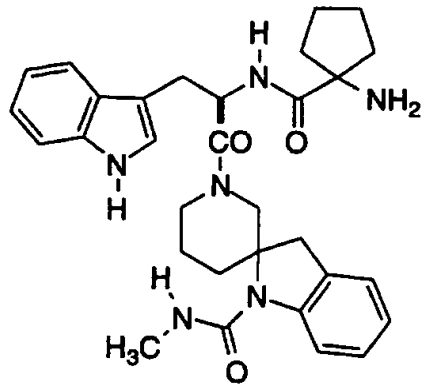


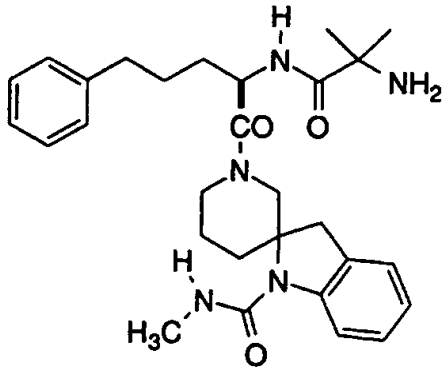


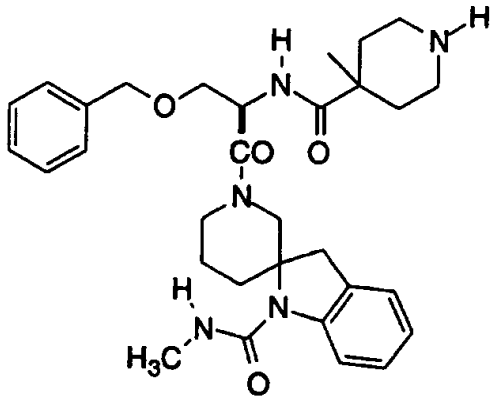


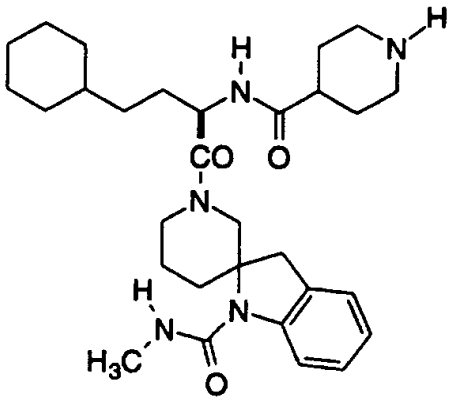


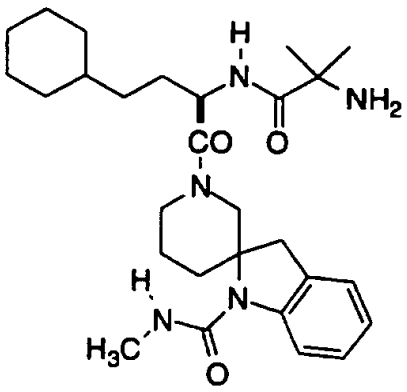


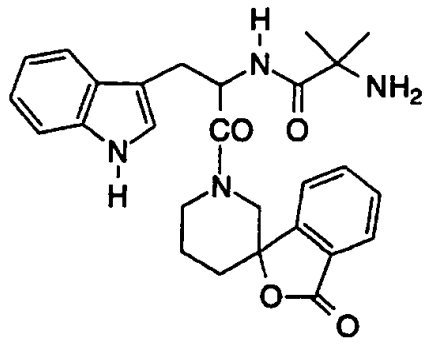


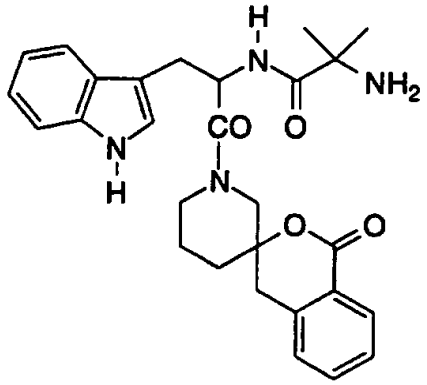


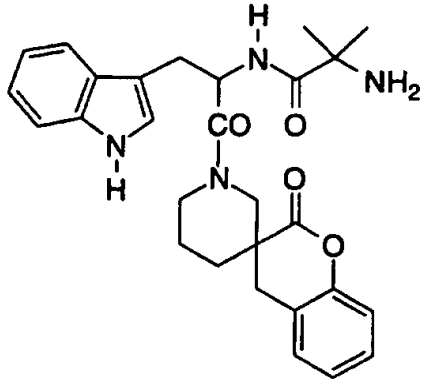


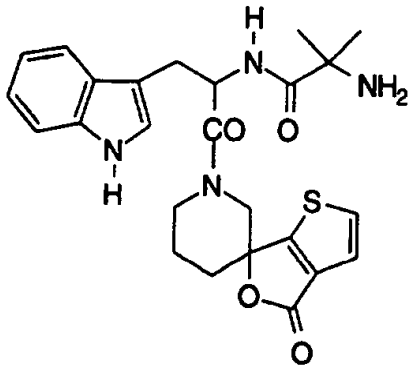


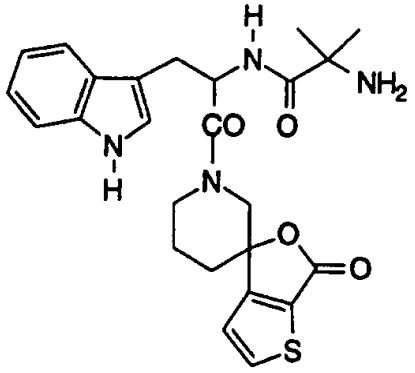


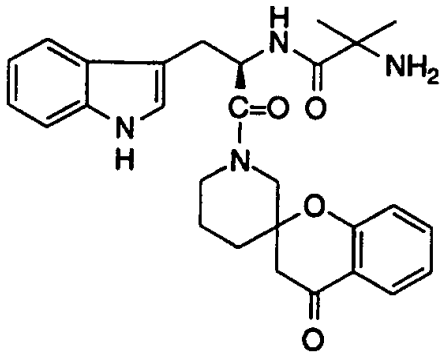


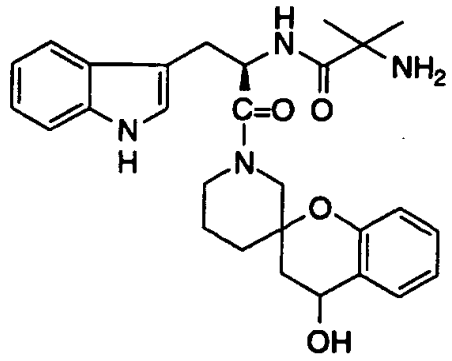


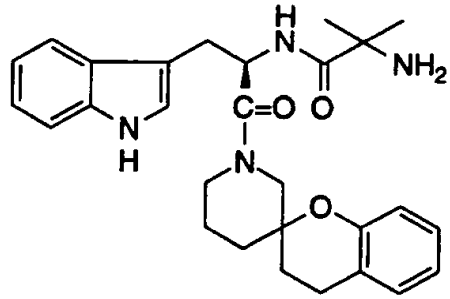


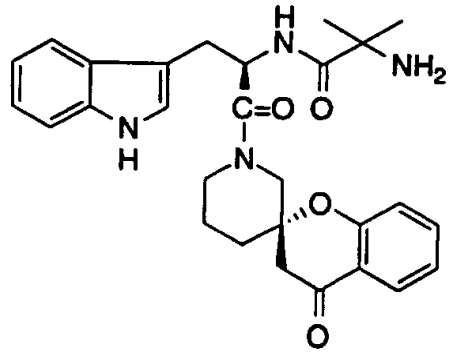


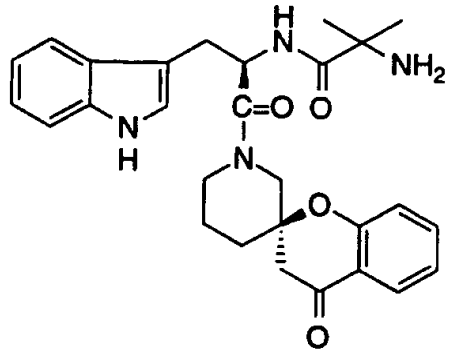


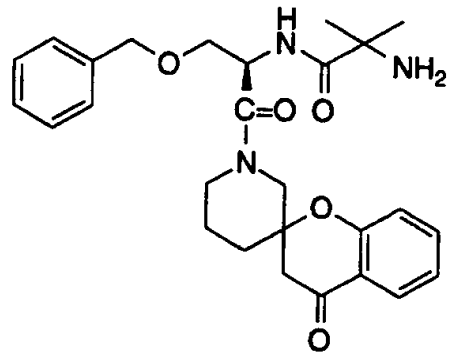


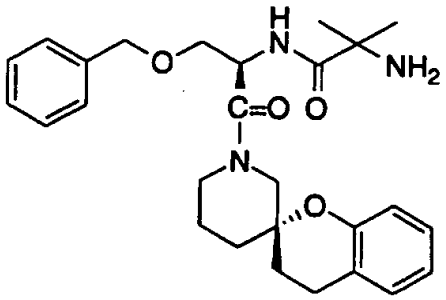


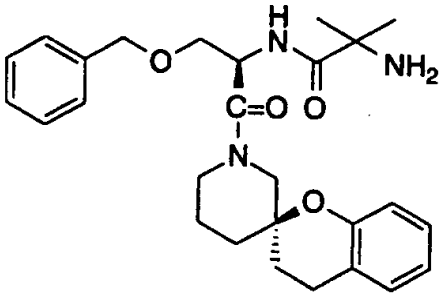


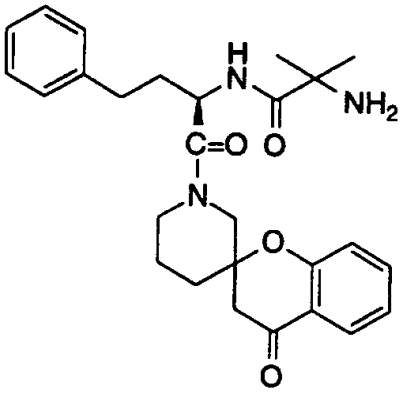


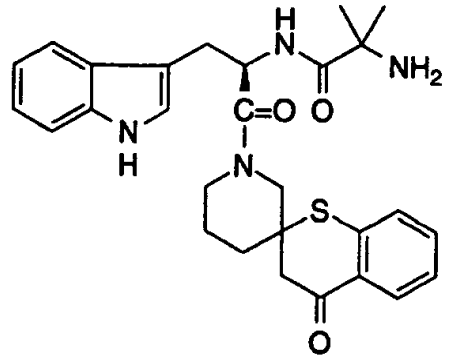


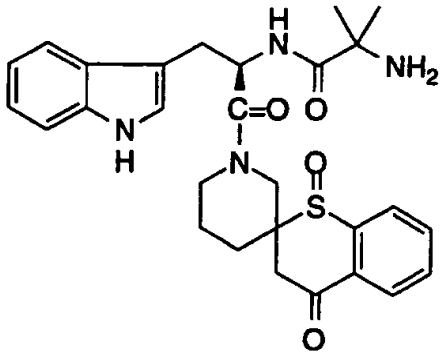


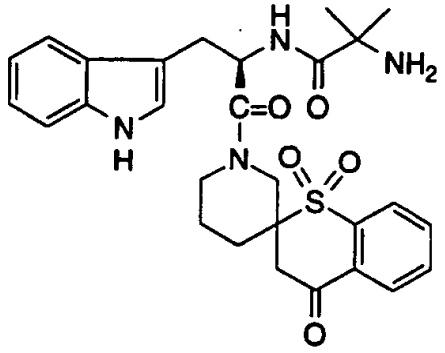












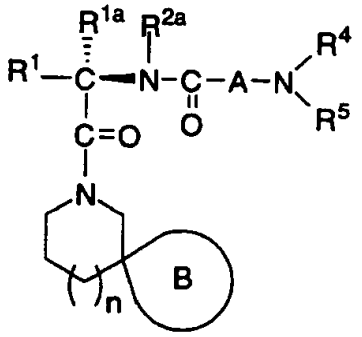
and pharmaceutically acceptable salts and individual diasteromers thereof.

Throughout the instant application, the following abbreviations are used with the following meanings:

Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
calc.	calculated
CBZ, Cbz	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
EI-MS	Electron ion-mass spectroscopy
Et	ethyl
eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
HOBT, HOBt	Hydroxybenztriazole
HPLC	High pressure liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MF	Molecular formula
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pr	propyl
prep.	prepared
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TMS	Tetramethylsilane

Asymmetric centers may be present in the compounds of the instant invention depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixture and as pure or partially purified compounds are included within the ambit of this invention. In the case of the asymmetric carbon atom represented by an asterisk in Formula I, it has been found that compounds are more active as growth hormone secretagogues and, therefore preferred, in which the nitrogen substituent is above and the R^{1a} is below the plane of the structure as represented in Formula II. An equivalent representation places R^1 and the N-substitutent in the plane of the structure with the C=O group above. This configuration corresponds to that present in a D-amino acid. In most cases, this is also designated an R-configuration, although this will vary according to the value of R^1 used in making R- or S- stereochemical assignments. In the case of the asymmetric center which bears the spirolactam or spiroamine, in most cases, both R- and S- configurations are consistent with useful levels of growth hormone secretagogue activity. In addition, configurations of some of the most preferred compounds of this invention are indicated. When the carbon atom in Formula I bearing an asterisk is of a defined and usually a D-configuration, two diastereomers result according to the absolute configuration at the carbon atom bearing the spirolactone if no additional stereo centers are present. These diastereomers are arbitrarily referred to as diastereomer 1 (d_1) and diastereomer 2 (d_2) in this invention and, if desired, their independent syntheses or chromatographic separations may be achieved as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.



Formula II

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, the open form of the lactones may be isolated as their inorganic salts in which the counterion is selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

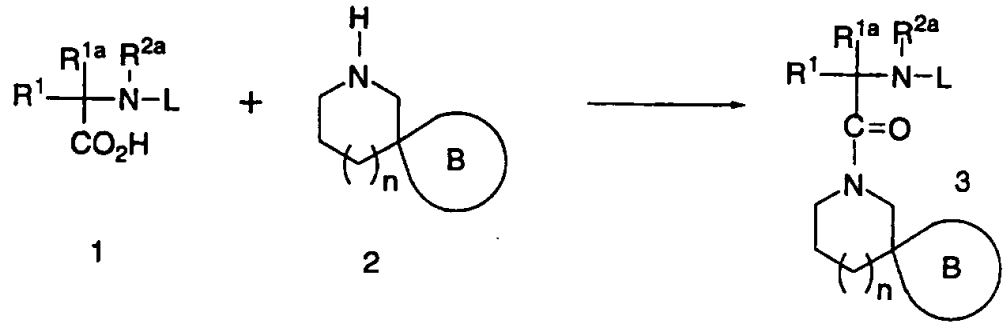
The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of

methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a nobel metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines and pyrrolidines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures includes crystallization, normal phase or reverse phase chromatography.

SCHEME 1

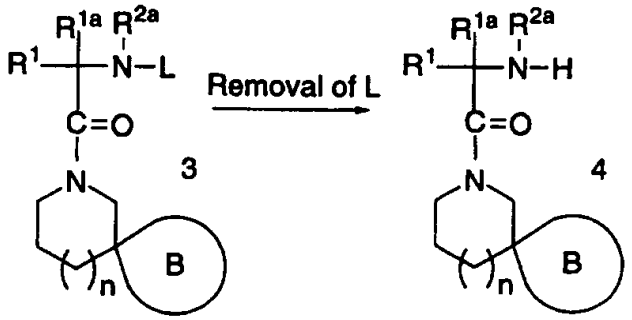


1 2

Intermediates of Formula 3 may be synthesized as described in Scheme 1. Coupling of the pyrrolidine or piperidine amine of Formula

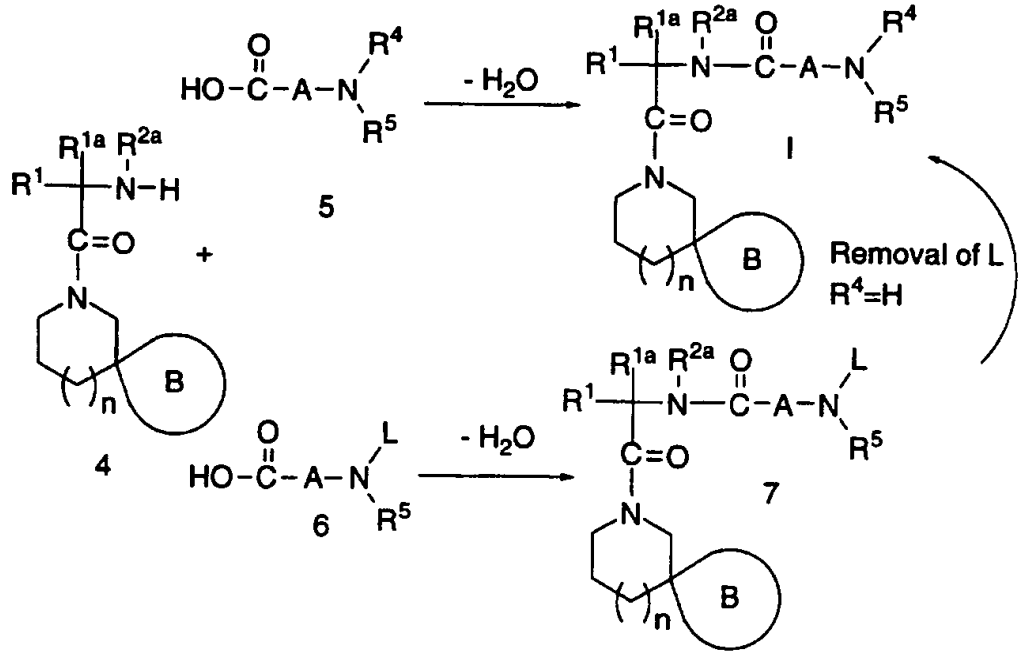
2, whose preparations are described later if they are not commercially available, to protected amino acids of Formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

SCHEME 2



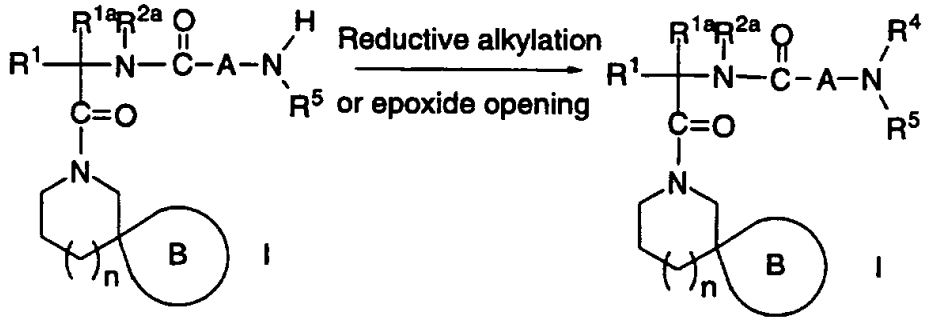
Conversion of 3 to intermediate 4 can be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)

SCHEME 3



Intermediates of Formula 5, wherein A is -$(CH_2)_x$-$C(R^7)(R^{7a})$-$(CH_2)_y$- may be coupled to intermediates of Formula 4 to afford compounds of Formula I under standard peptide coupling reaction conditions. The amino acids 5, as amino acid 1, are either commercially available or can be synthesized by routine methods. Also if R^4 or R^5 is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein L is a protecting group as defined above. The removal of L in 7 to afford I, where R^4 = H, can be carried out as noted above.

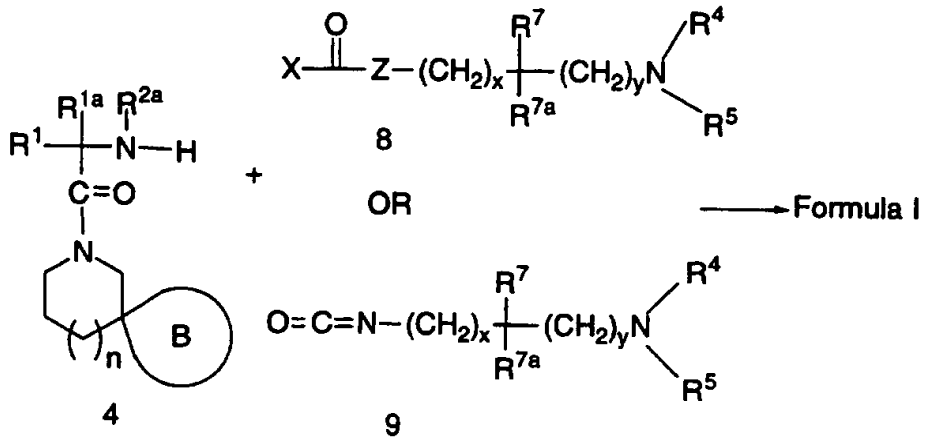
SCHEME 4



(where R^4 is substituted/ unsubstituted alkyl)

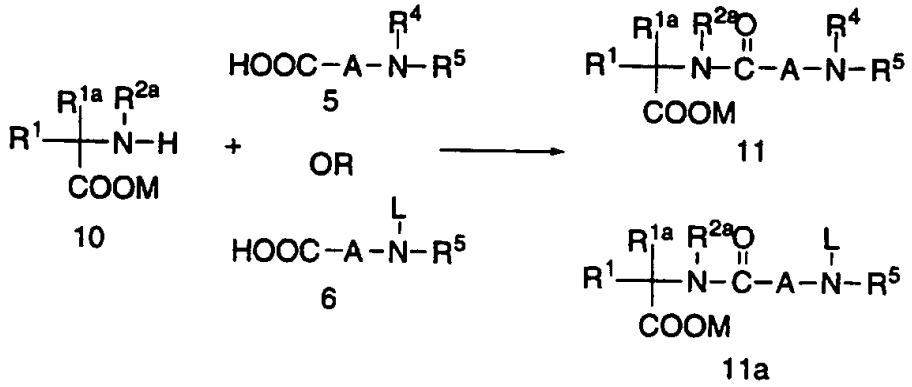
Compounds of Formula I wherein R^4 and/or R^5 is a hydrogen may be further elaborated to other Compounds of Formula I (with side chains R^4 = R^2 or CH_2-CH(OH)-CH_2X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

SCHEME 5



Compounds of Formula I, wherein A is Z-$(CH_2)_x$-$C(R^7)(R^{7a})$-$(CH_2)_y$ and Z is N-R6a or O may be prepared as shown in Scheme 5 by reacting 4 with reagents 8, wherein X is a good leaving group such as Cl, Br, I, or imidazole. Alternatively, 4 may be reacted with an isocyanate of Formula 9 in an inert solvent such as 1,2-dichloroethane to provide compounds of Formula I where Z is NH. The R^4 group in reagents 8 and 9 may be protected with a protecting group L, which is subsequently removed.

SCHEME 6

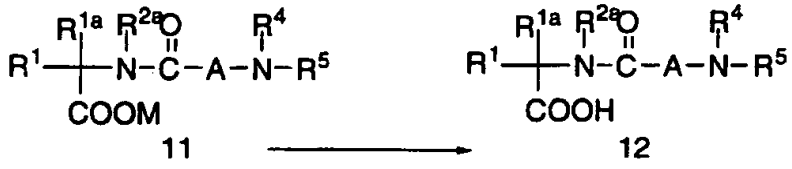


The compounds of general Formula I of the present invention may also be prepared in a convergent manner as described in reaction Schemes 6, 7 and 8.

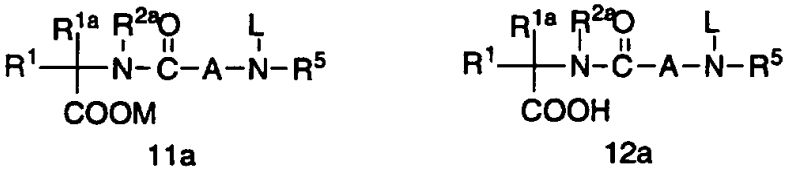
The carboxylic acid protected amino acid derivatives 10 are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of the amino acid with an alcohol in the presence of an acid such as hydrochloric acid or p-toluenesulfonic acid and azeotropic removal of water. Other reactions includes the reaction of a protected amino acid with a diazoalkane, or with an alcohol and an acid activating agent such as EDC, DCC in the presence of a catalyst such as DMAP and removal of the protecting group L.

Intermediates of Formula 11 or 11a, may be prepared as shown in Scheme 6 by coupling of amino acid ester 10 to amino acids of Formula 5 or 6. When a urea or carbamate linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 5.

SCHEME 7



11 12

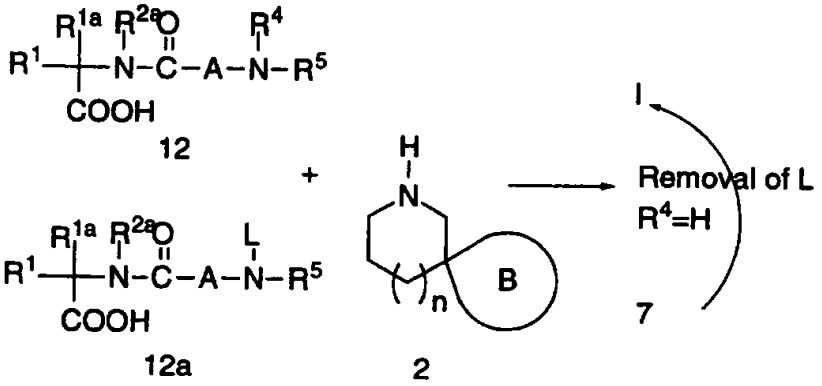


11a 12a

Conversion of the ester 11 or 11a to intermediate acids 12 or 12a may be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by

a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see J. Org. Chem., 42, 587 (1982)).

SCHEME 8

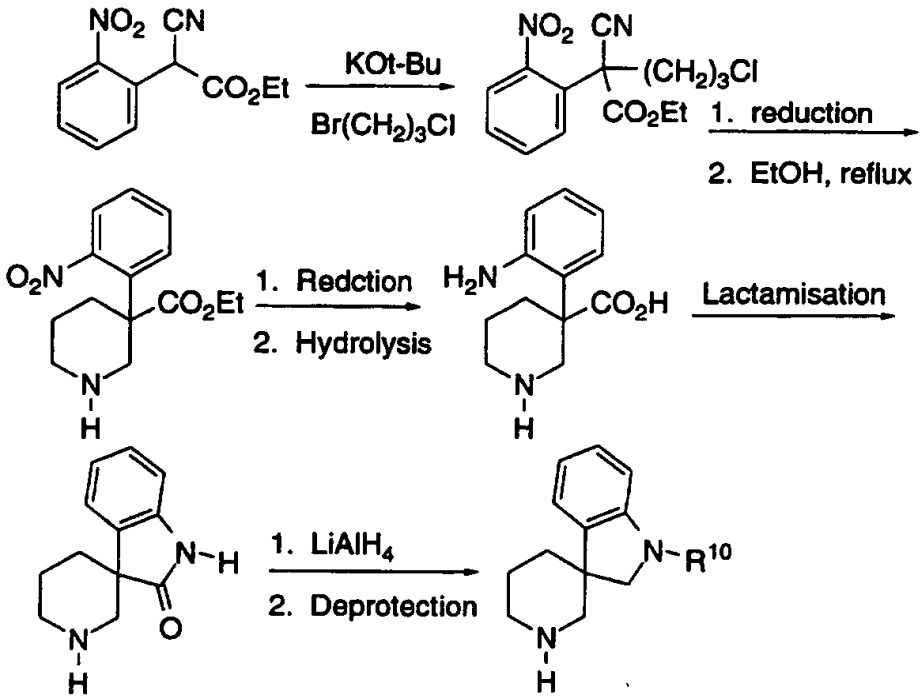


Acid 12 or 12a may then be elaborated to I or to I bearing protecting group L (Compound I) as described in Scheme 8. Coupling of piperidines and pyrrolidines of Formula 2 to acids of Formula 12 or 12a, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of 7 to I is achieved by removal of the protecting group L. When R4 and/or R5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

The introduction of spirolactams, spiroamines, spirolactones, spirobenzopyrans, spirobenzothiopyransn spirobenzofurans, and spirobenzothiophenes in the 3-position of the piperidine or the pyrrolidine may be achieved from cyano, ester, amide and ketone substituents in that position and is conducted by methods known in the art. Such methods are illustrated in the following schemes for piperidines. Analogous methods may be used for the preparation of the pyrrolidine compounds. Similar strategies may be used in the preparation of thiophene, furan and thiazole analogs. In the interest of clarity, the benzo rings in the following

schemes are depicted as being unsubstituted. Compounds bearing additional substituents on the benzo rings are readily prepared by minor modification of the methods herein with procedures known in the art.

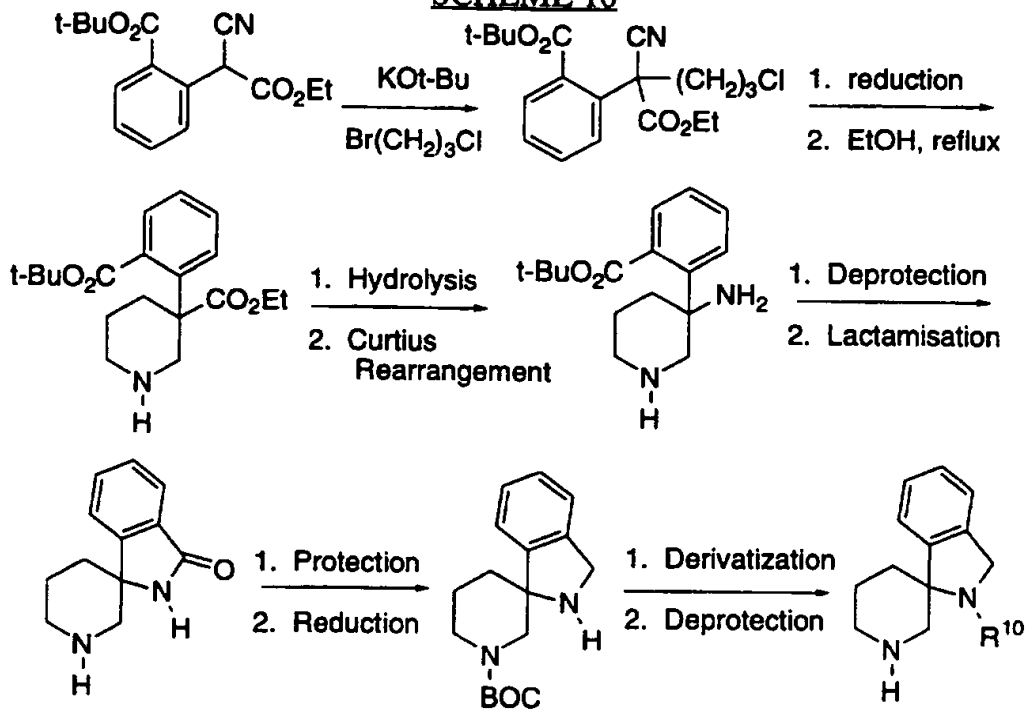
SCHEME 9



3-Spiroamides and 3-spiroamines may be synthesized as shown in Scheme 9. This procedure essentially follows the general protocols of Jacoby et. al., J. Med. Chem. 24, 281 (1981). Alkylation of ethyl-5-chloro-2-cyano-2-(o-nitrophenyl) valerate with 1-bromo-3-chloropropane and potassium t-butoxide gives the nitrile. Selective reduction of the nitrile to the amine may be accomplished by methods known in the art such as reduction with H_2/Pd catalysis. The chloride is displaced by refluxing in a high boiling solvent such as ethanol to give the piperidine. The ethyl ester is hydrolyzed to the acid under basic conditions and the nitro group is reduced to the amine by methods known in the art such as catalytic hydrogenation to give the amino acid. The amino acid is cyclized to the 3-spiroamide. The 3-spiroamide is

protected and the amide group reduced by methods known in the art for example by $LiAlH_4$. Derivatisation of the amine is achieved by reaction with an appropriate acylating reagent, sulfonylating reagent, or an isocyanate. The protecting group is removed by treating the N-BOC derivative with TFA or HCl to give the desired 3-spiroamine.

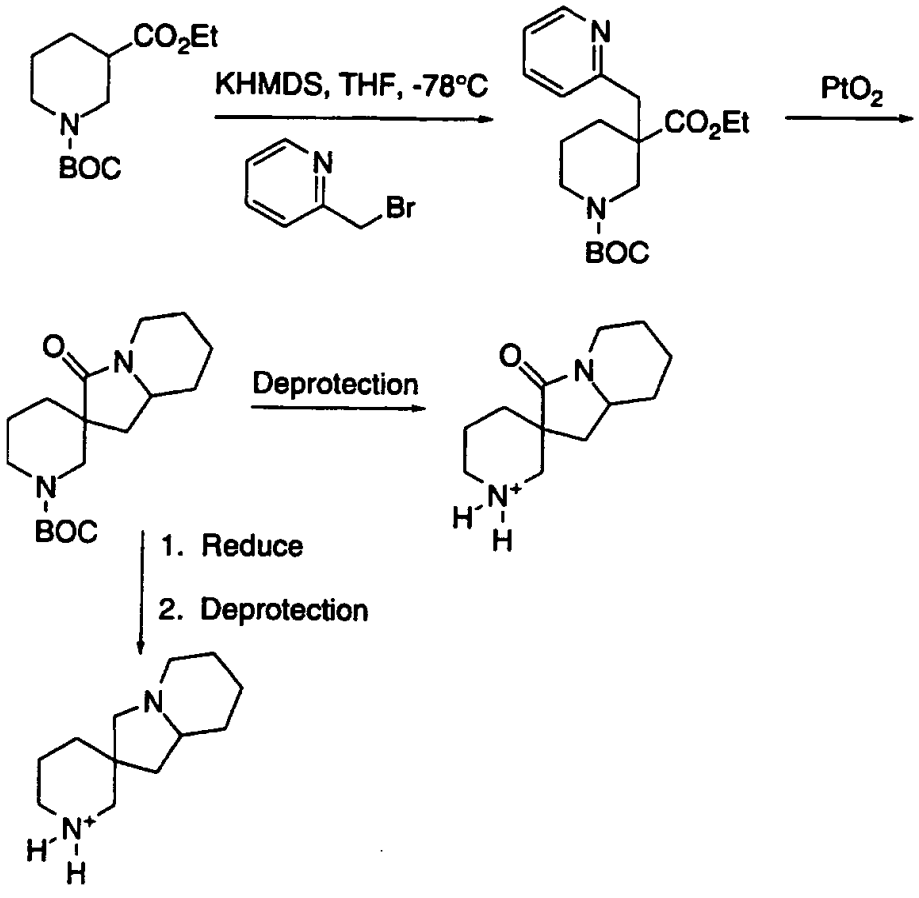
SCHEME 10



3-Spiroamides and 3-spiroamines may also be synthesized as shown in Scheme 10. This procedure essentially follows the general protocols of Jacoby et. al., J. Med. Chem. 24, 281 (1981). Alkyaltion of ethyl-5-chloro-2-cyano-2-(o-t-butoxycorbonylphenyl) valerate with 1-bromo-3-chloropropane and potassium t-butoxide gives the nitrile. The selective reduction of the nitrile to the amine may is accomplished by methods known in the art for example by catalytic reduction with H_2/Pd. The chloride is displaced by refluxing in a high boiling solvent such as ethanol to give the piperidine. The ethyl ester is hydrolyzed to the acid under basic conditions to give the carboxylic acid and the carboxylic acid is converted to the amine by methods known in the art to give the ester. The tert-butyl ester group is deprotected by treatment with a strong acid

such as HCl or TFA to give the 3-spiroamide. The piperidine nitrogen is protected as its N-BOC derivative and the amide is reduced by treatment with borane to give the 3-spiroamine. Derivatization of the amine is achieved by reaction with the appropriate acylating reagent, sulfonylating reagent, or isocyanate. The protecting group is removed by treatment of the N-BOC derivative with strong acid such as HCl or TFA to give the 3-spiroamine compound.

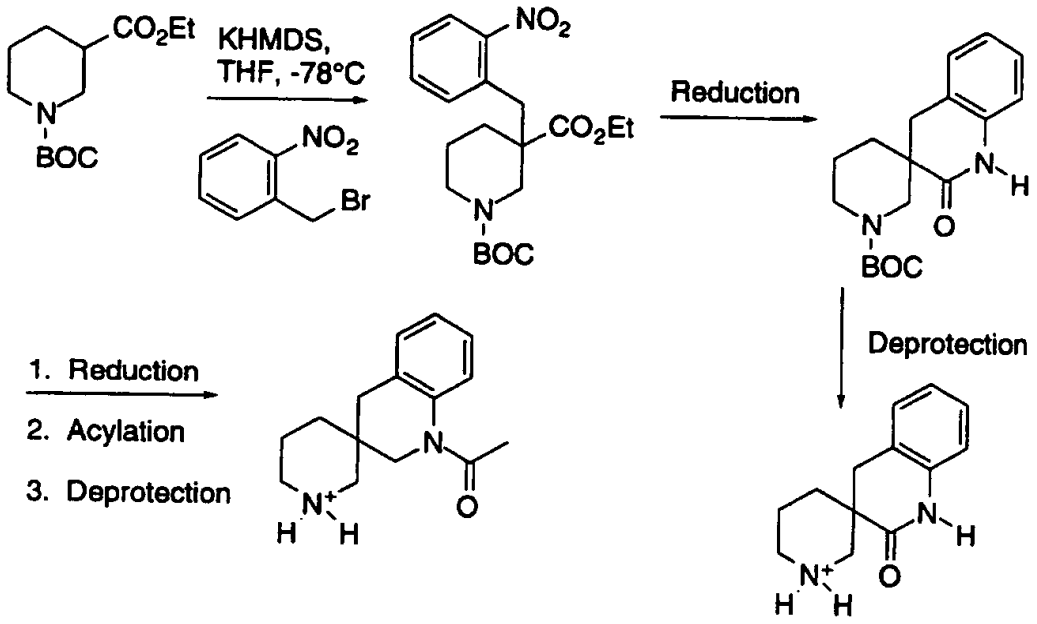
SCHEME 11



The 3-spiroamide and 3-spiroamine may also be synthesized in the manner outlined in Scheme 11. N-BOC ethyl nipecotate is alkylated with 2-pyridine benzyl bromide to give the ester. Reduction of the pyridine group by catalytic hydrogenation with PtO_2 as a catalyst

gives the indicated spirocycle. The protecting group of the 3-spiroamide is removed by treatment of the N-BOC derivative with a strong acid such as HCl or TFA. Alternatively, reduction of the 3-spiroamide with borane gives the 3-spiroamine after deprotection of the N-BOC protecting group.

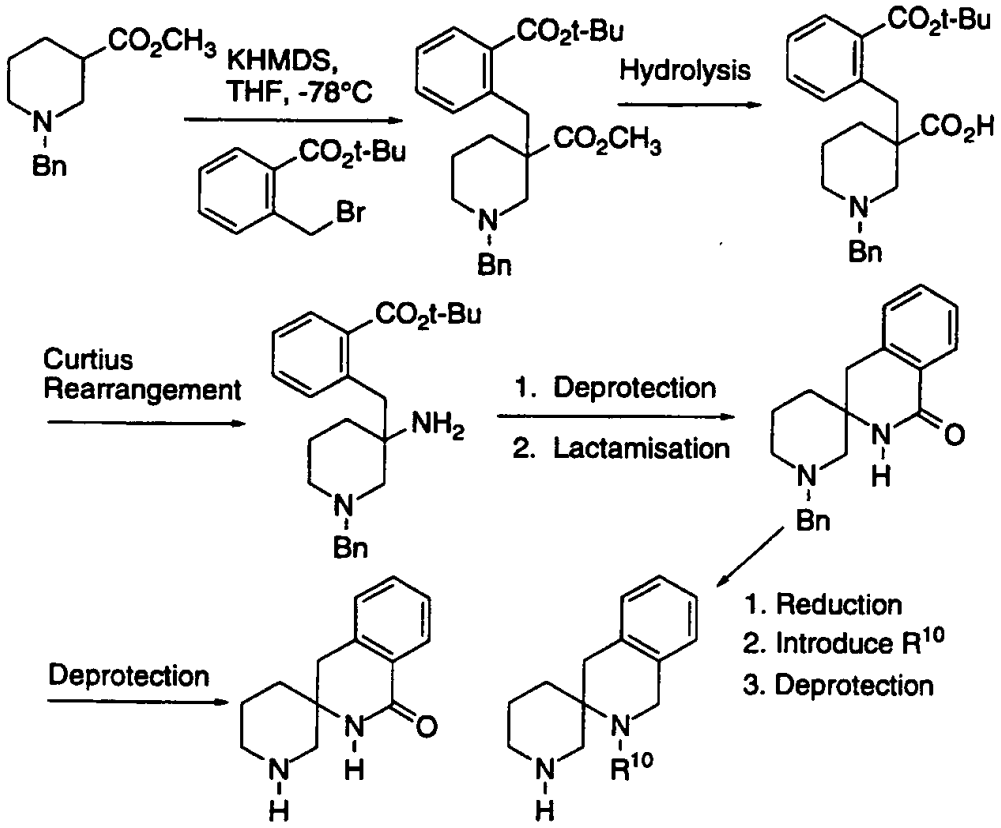
SCHEME 12



3-Spiroamdes and 3-spiroamines of the general formula of may also be synthesized as shown in Scheme 12. N-BOC ethyl nipecotate is alkylated with 2-nitrobenzyl bromide to give the ester derivative. Reduction of the aromatic nitro group with H_2/Pd/C gives the aniline derivatve. The ethyl ester is hydrolyzed under basic conditions to give the carboxylic acid. The aniline derivative is cyclized by treatment of the carboxylic acid with a coupling reagent such as EDCI to give the 3-spiroamide. The 3-spiroamide is deprotected by treatment with a strong acid such as HCL or TFA to give the amine salt. Alternatively, the 3-spiroamide is reduced by treatment with borane THF complex to give the 3-spiroamine. Derivatization of the amine is achieved by reaction with the appropriate acylating reagent, sulfonylating

reagent, or isocyanate. The protecting group is removed by treatment of the N-BOC derivative with strong acid such as HCl or TFA to give the 3-spiroamine.

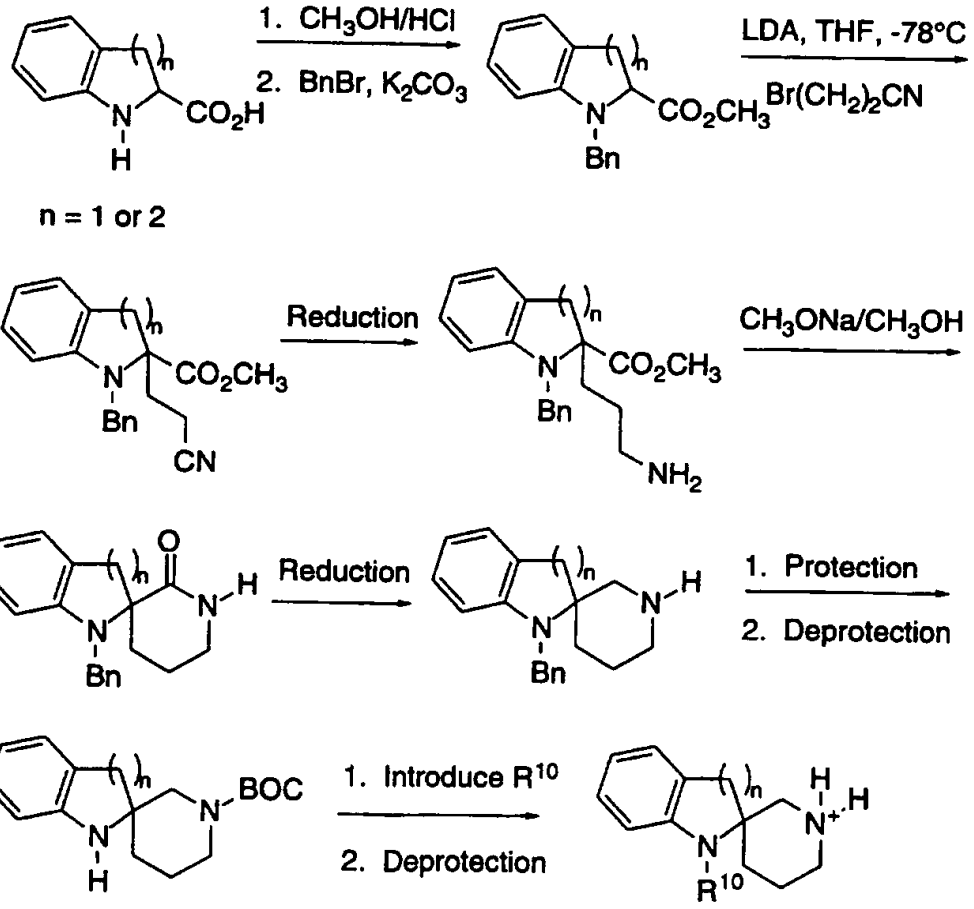
SCHEME 13



3-Spiroamides and 3-spiroamines are also synthesized as shown in Scheme 13. N-BOC methyl nipecotate is alkylated with 2-tert-butylcarboxy benzyl bromide to give the ester. Hydrolysis of the methyl ester is achieved under basic conditions to give the carboxylic acid. Conversion of the carboxylic acid to the amine may be achieved by methods known in the art. The tert-butyl ester is deprotected by treatment with a strong acid such as TFA or HCl to give the carboxylic acid. The carboxylic acid is cyclized to the 3-spiroamide of the general formula xx by treatment with EDCI or DCC. The amide is deprotected

by treatment of the N-BOC derivative with a strong acid such as TFA to give the amine salt. Alternatively, the 3-spiroamide is reduced by treatment with a reducing agent such as borane dimethyl sulphide to give the 3-spiroamine. Derivatization of the amine is achieved by reaction with the appropriate acylating reagent, sulfonylating reagent, or isocyanate. The protecting group is removed by treatment of the N-BOC derivative with strong acid such as HCl or TFA to give the 3-spiroamine derivative.

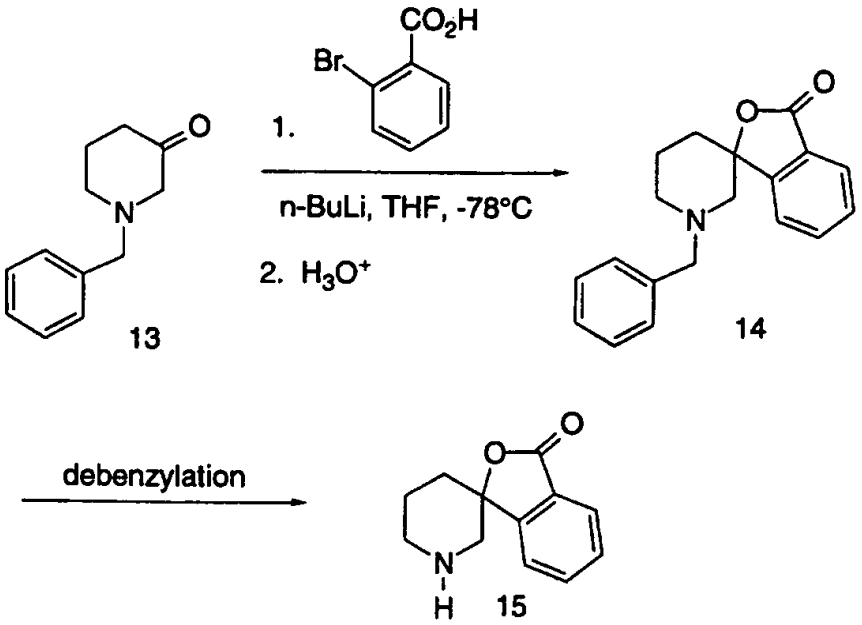
SCHEME 14



3-Spiroamides and 3-spiroamines are also synthesized as shown in Scheme 14. Fischer esterification of the carboxylic acid with HCl and methanol (n=1 or 2) followed by protection of the aniline as its

benzyl amine by treatment with benzyl bromide and a base such as potassium carbonate gives the ester (n=1 or 2). Deprotonation of the ester with a strong base such as LDA or KHMDS followed by quenching the ester enolate with 1-bromo-proprionitrile gives the nitrile (n=1 or 2). Selective reduction of the nitrile with H_2/PtO_2 at 40 psi gives the amine which is cyclized to the spiroamide by treatment with a base such as sodium methoxide. The amide is reduced with borane/THF complex or borane dimethyl sulphide to give the amine. The amine is protected as its N-BOC derivative. Removal of the benzyl group is accomplished by treatment with H_2, 10% Pd/C to give the aniline derivative. Derivatization of the aniline is achieved by reaction the appropriate acylating reagent, sulfonylating reagent, or isocyanate. The N-BOC protecting group is then removed by reaction with a strong acid such as HCl of TFA to give the amine salt.

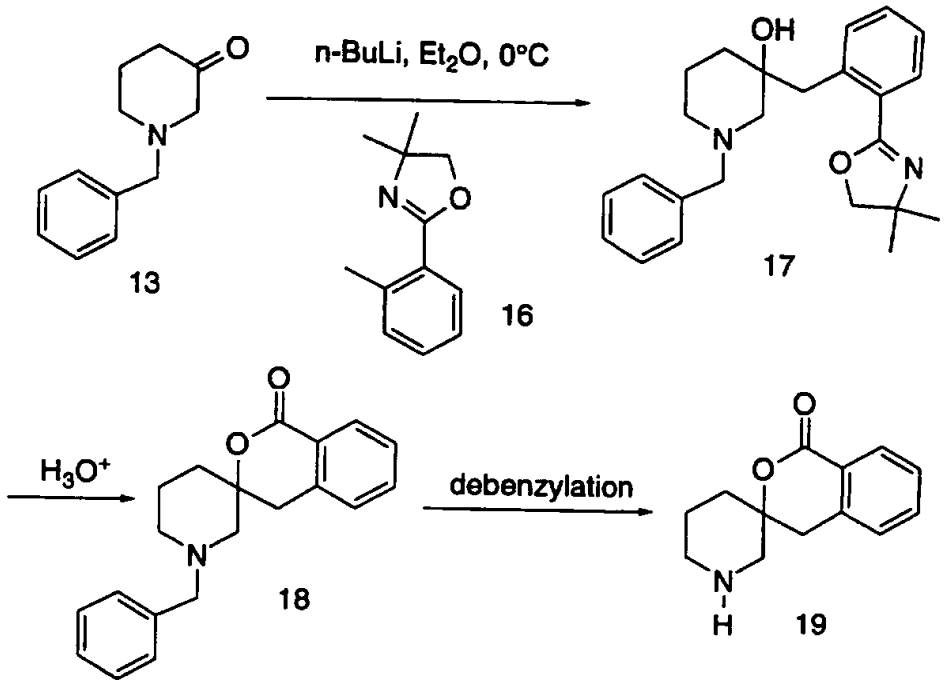
SCHEME 15



The spiro lactone 15 may be prepared by the method originally described by Parham and coworkers (*J. Org. Chem.* 1976, *41*, 2628). Addition of the appropriately substituted Grignard reagent or organolithium reagent to the starting ketone 13 as shown in Scheme

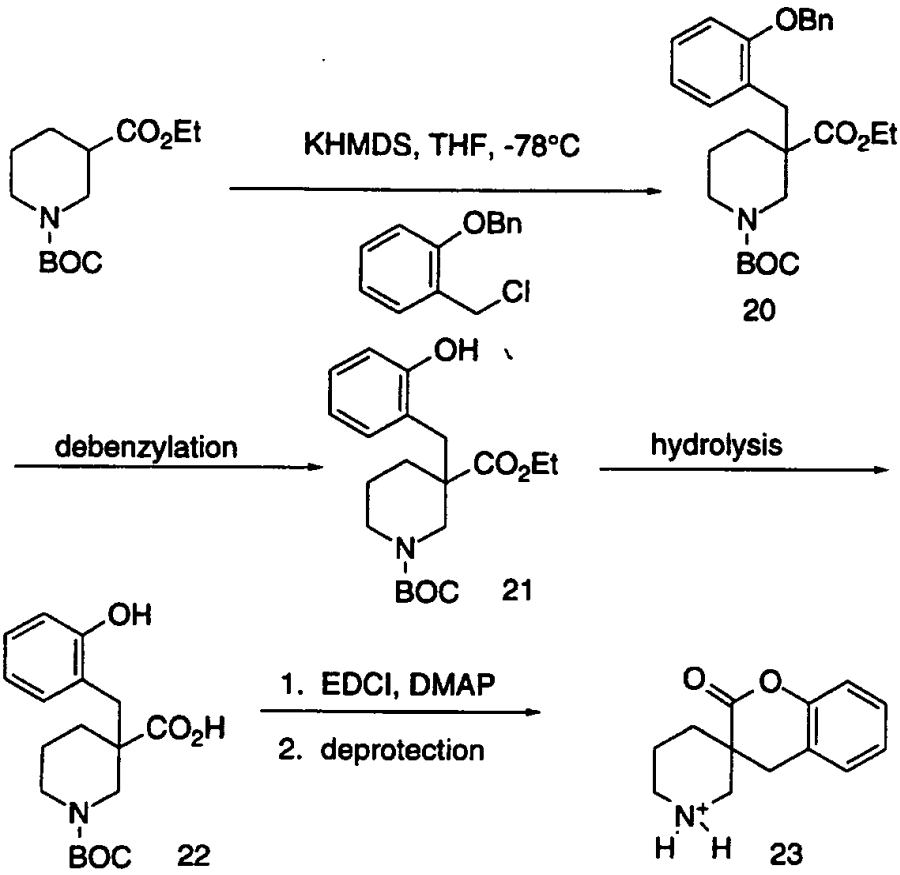
15 followed by mild acid treatment gives the 3-spirolactone 14. The removal of the benzyl protecting group may be accomplished by methods known in the art, such as catalytic hydrogenolysis or using chloroethyl chloroformate followed by hydrolysis, to give the spirolactone 15.

SCHEME 16



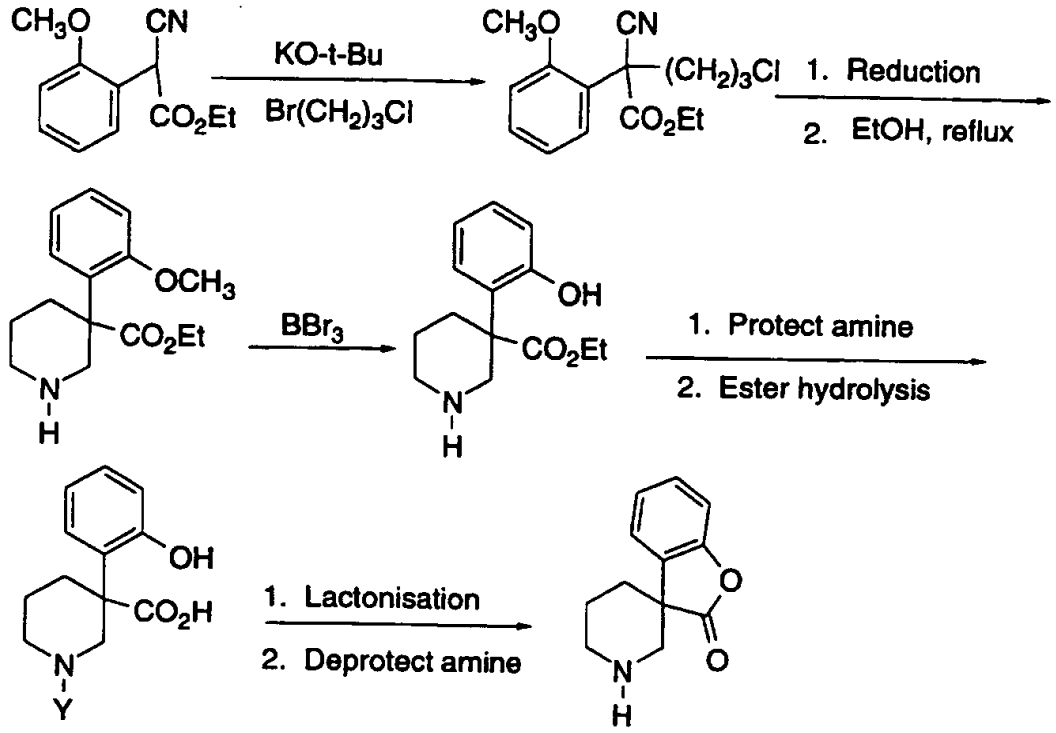
An alternative method for the synthesis of 3-spiro lactones in the 3-position of a piperidine or pyrrolidine 14 is illustrated in Scheme 16 and has been described by Fu and coworkers (*J. Org. Chem.* 1985, *50,* 1259). Addition of the benzylic anion generated from the oxazoline 16 to the ketone 13 gives the alcohol 17. The alcohol 17 is hydrolysed with a mild acid to give the lactone 18. Removal of the benzyl group is accomplished by methods as described above to give the spirolactone 19.

SCHEME 17



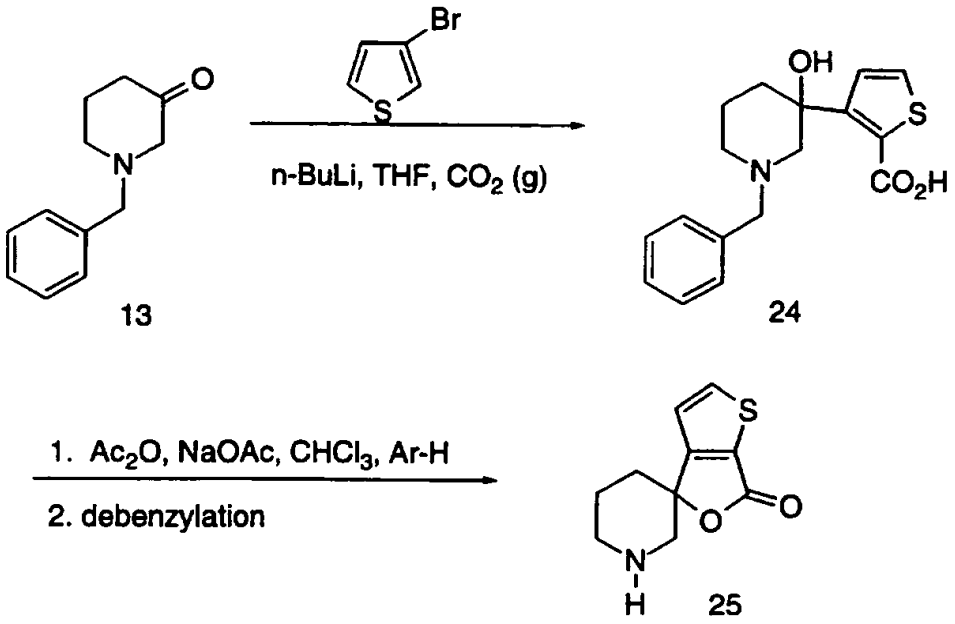
The synthesis of piperidines or pyrrolidines with a 3-spirolactone 23 is illustrated in Scheme 17. Alkylation of the appropriately protected ethyl nipcotate with the appropriately substituted alkylating reagent gives the ester 20. Removal of the benzyl protecting group by hydrogenolysis gives the phenol 21. Hydrolysis of the ester on 21 gives the carboxylic acid 22. The acid 22 is lactonised by methods known in the art including that involving activation using EDCI/DMAP and removal of the nitrogen protecting group as described above gives the 3-spirolactone 23.

SCHEME 18



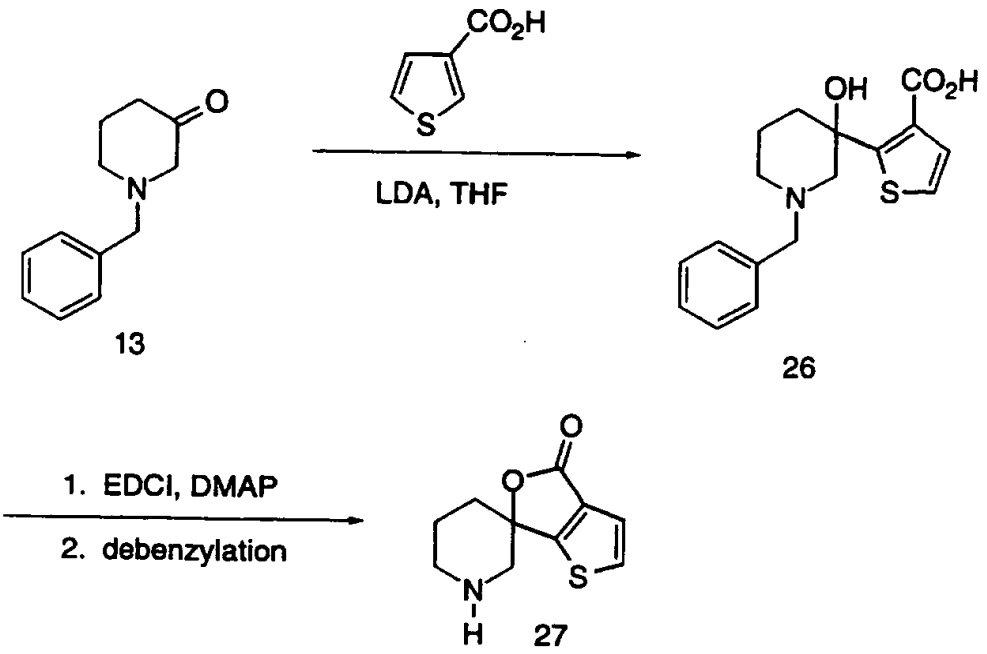
The preparation of piperidines and pyrrolidines with a 3-spirolactone is described in Scheme 18 (see Jacoby et. al., *J. Med. Chem.* 1981, *24*, 218). Ethyl 5-chloro2-cyano-2-(o-methoxyphenyl)-valerate is alkylated with 1-bromo-3-chloropropane and potassium t-butoxide to give the indicated nitrile. The nitrile is reduced to the amine by methods known in the art. The chloride is displaced by refluxing in ethanol or any other high boiling solvent to give the piperidine and the methyl group is removed by treatment with boron tribromide to give the indicated phenol. Following protection of the amine (if necessary, for example with a BOC protecting group) by methods known in the art, the ethyl ester is hydrolysed to give the carboxylic acid. The acid is lactonised by methods known in the art to give the lactone. The protecting group, if present, is removed by methods known in the art to give the amine.

SCHEME 19



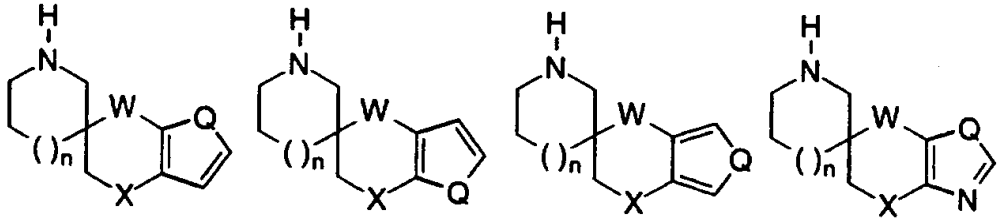
The synthesis of piperidines and pyrrolidines with a 3-spirolactone 25 is illustrated in Scheme 19 and has been described by Sauter and coworkers (Heterocycles 1987, *26*, 2639). Addition of the 3-bromo thiophene to an appropriately protected piperidine gives the hydroxy acid 24. Lactonisation is achieved using acetic anhydride and sodium acetate, and removal of the nitrogen protecting group by the methods described earlier gives the 3-spirolactone 25.

SCHEME 20



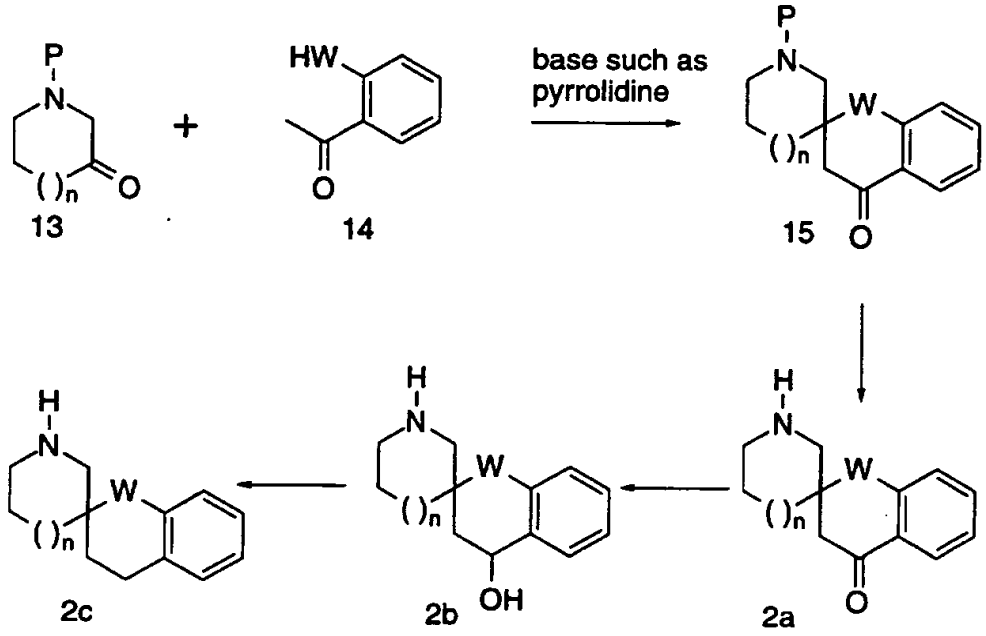
The synthesis of piperidines and pyrrolidines with a 3-spirolactone 27 is illustrated in Scheme 20 and has been described by Sauter and coworkers (Heterocycles *26*, 2639 (1987)). Addition of the 3-thiophene carboxylic acid to an appropriately protected piperidine gives the hydroxy acid 26. Lactonisation and removal of the nitrogen protecting group is achieved as above to give the 3-spirolactone 27.

FIGURE A



In the interest of clarity, benzo functionality is shown in the following schemes and such functionality is depicted as being unsubstituted. Compounds bearing additional substituents on the benzo or other rings are readily prepared by minor modification of the methods herein with procedures known in the art. In Figure A and in subsequent schemes n = 0 or 1.

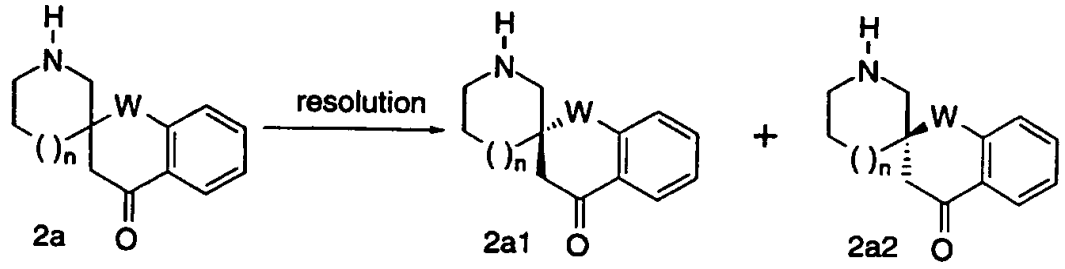
SCHEME 21



As illustrated in Scheme 21, the spiro[3H-1-benzopyran-2,3'-piperidine] (where W=O in general formula 2) analogs can be prepared from a substituted or unsubstituted 2-hydroxyacetophenone and a properly protected 3-piperidone (such as N-benzyl 3-piperidone which is commercially available, where n=1 in general formula 2) as described by Kabbe, H. J. Synthesis 1978, 886-887 and references cited therein. The 2-hydroxyacetophenones, in turn, are either commercially available or can be prepared by routes in the literature known to those skilled in the art. Such methods are described by Chang, C. T. et al, in J. Am. Chem. Soc., 1961, 3414-3417 and by Elliott, J. M. et al, in J. Med. Chem. 1992, 35, 3973-3976. Removal of the protecting group as described in:

Protective Groups in Organic Synthesis, Greene, T. W., Wuts, P. G., John Wiley & sons, New York, 1991, and Olofson, R.A. et al, J. Org. Chem. 1984, 49, 2081-2082, provides the benzopyranone 2a. The ketone functionality in compounds of general structure 2a may be reduced to an alcohol 2b using sodium borohydride or may be fully reduced to a methylene also employing conditions known to those skilled in the art. For example, reduction of the ketone with sodium borohydride, followed by palladium hydroxide catalyzed hydrogenation yield compounds with general structure 2c. The amine of structure 2a-c can then be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8 utilizing generic formula 2. Alternatively, the ketone can often be reduced after incorporation into the compounds of Formula I. Similarly, the spiro[3H-1-benzothiopyran-2,3'-piperidine] (where W=S in general formula 2) analogs can be prepared from by substituting 2-hydroxyacetophenone with 2-mercaptoacetophenone.

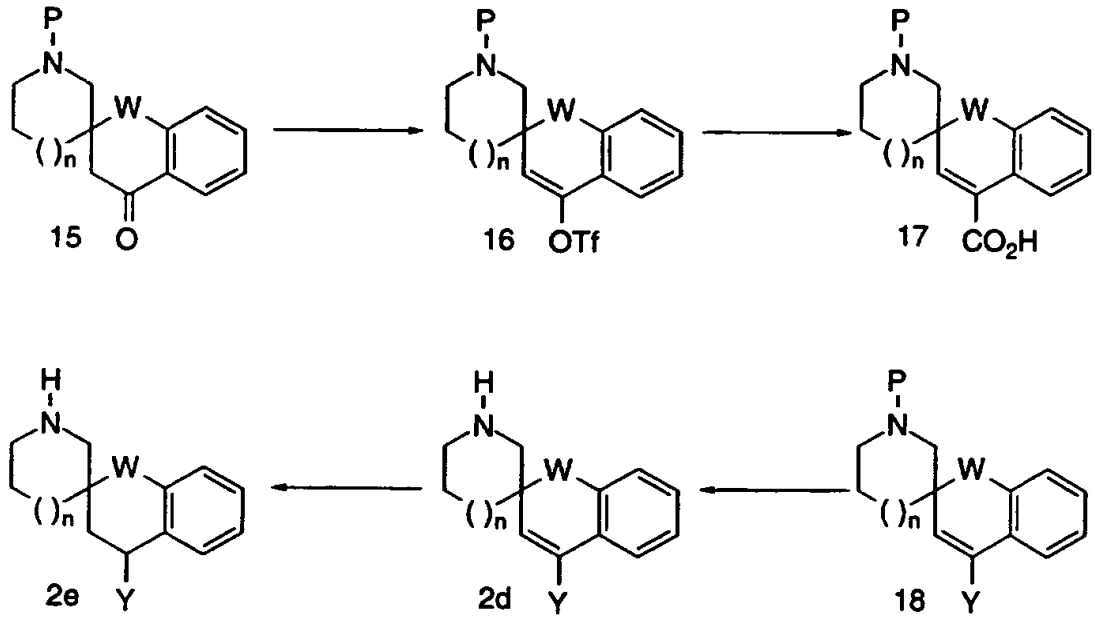
SCHEME 22



Compounds of the general formula 2 prepared in this way are racemic. As shown in Scheme 22 resolution of the two enatiomers can be conveniently achieved by classical crystallization methods by using a chiral acid such as L- or D-tartaric acid or (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine 2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis. Asymmetric alkylation can also be utilized for the synthesis of optically

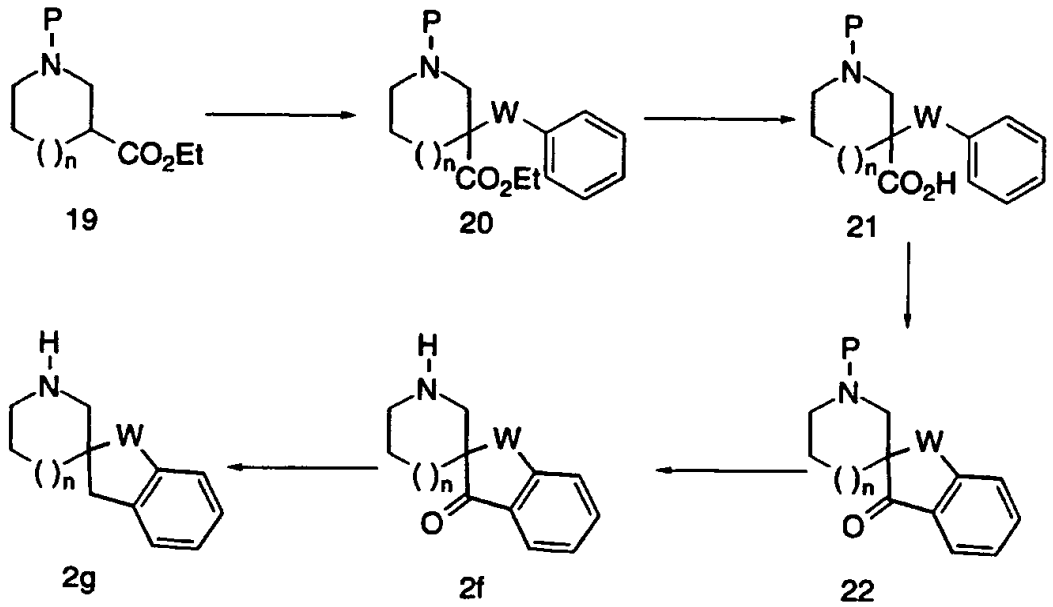
active intermediate by chiral amine catalysts for the spiro ring formation. Preparation of chiral hydroxyspiro[3H-1-benzopyran-2,3'-piperidine] analogs can be achieved using optically active reducing agents

SCHEME 23



As shown in Scheme 23 the incorporation of Y in to the benzopyranes of formula 15 can be achieved by modification of the ketone. Treatment of 15 with a base in an inert solvent such as THF followed by the addition of a triflating agent provides the enol triflate 16. Carboxylation of the enol triflate according to the procedure of Cacchi, S. Tetrahedron Letters, 1985, 1109-1112 provides an ester which was saponified to yield the acid 17. The carboxylic acid 17 then can be derivatized to afford amides or esters as defined by Y. The protecting group can then be removed as described above and the resulting amine can be incorporated into a secretagogue via the chemistry depicted in Schemes 1 and 8. A secretagogue containing an acid function is readily available via saponification of the ester group as the final step of the synthesis .

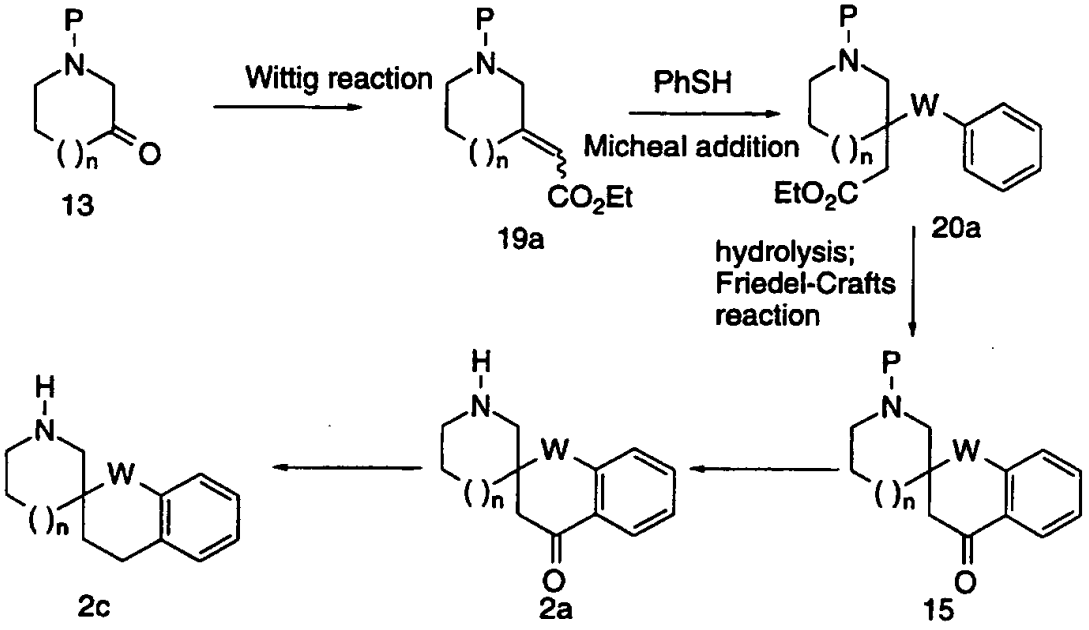
SCHEME 24



Spiro[3H-1-benzofuran-2,3'-piperidine] and spiro[3H-1-benzothiophene-2,3'-piperidine] can be prepared from properly N-protected ethyl nipecotates. Illustrated in Scheme 24 is a general way to prepare them. Compounds of Formula 19 can be prepared by introduction of a protecting group to the commercially available ethyl nipecotate. The protecting group can be a carbamate such as CBZ or benzoate and can be introduced using the conventional techniques. Introduction of the -WPh group can be achieved by first reacting compounds of Formula 20 with a strong base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide followed by addition of diphenyl disulfide in a inert solvent such as THF at temperatures from -100° to room temperature. Saponification of the resulting ester with a base such as sodium hydroxide at temperatures from room temperature to reflux in aqueous ethanol. Friedel-Crafts reaction of the resulting acid 21 under the established conditions forms the spiro ring system. The

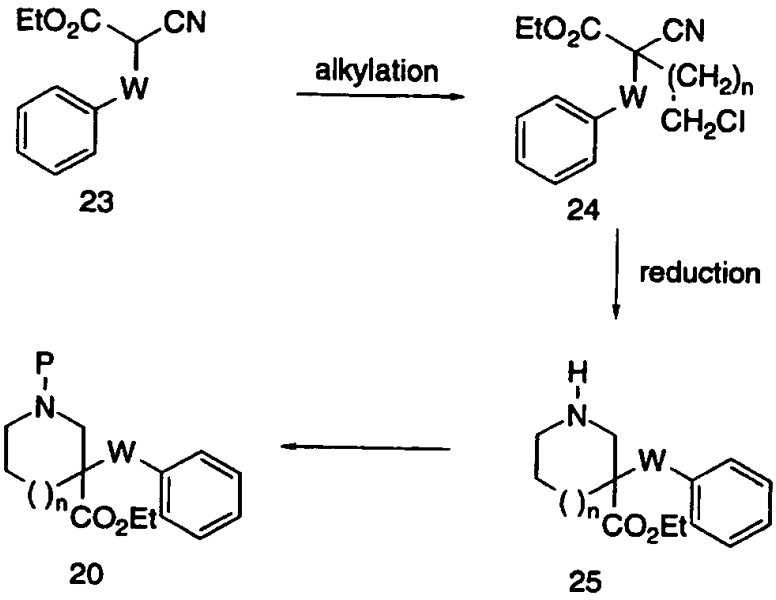
resulting ketone 22 can be converted to compounds of general structure 2f and 2g under conditions described above.

SCHEME 25



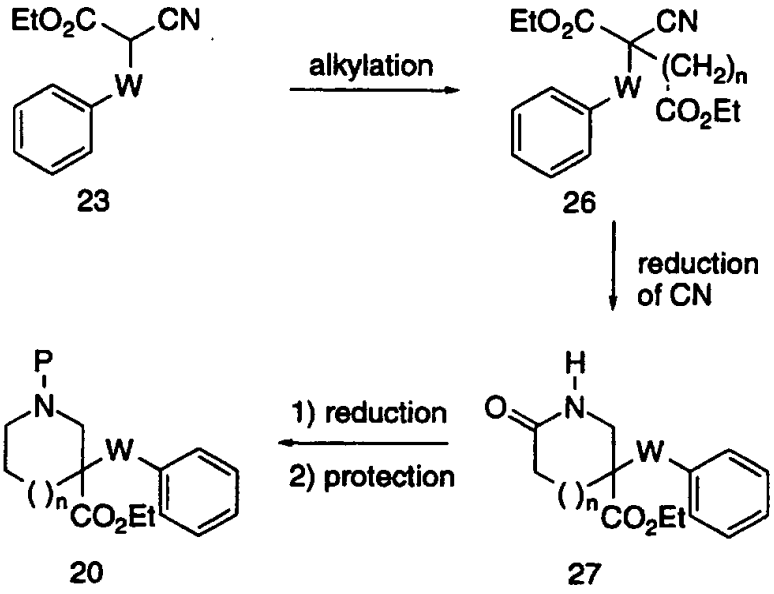
Spiro[3H-1-benzothiopyran-2,3'-piperidine] and spiro[3H-1-benzopyran-2,3'-piperidine] may be prepared from the sequence of a Wittig reaction, followed by a Michael addition and followed by a Friedel-Crafts reaction as shown in Scheme 25.

SCHEME 26



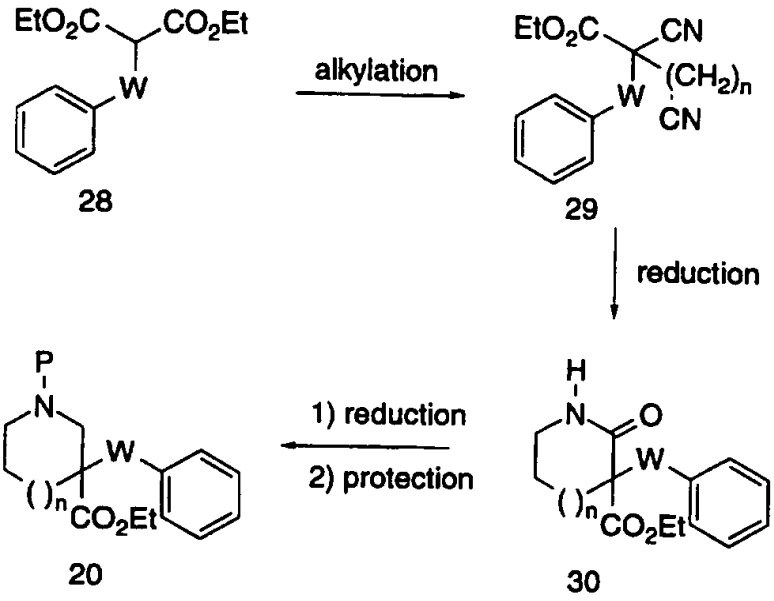
As shown in Scheme 26, additional methods for preparing compounds of structure 20 include construction of the ring itself (Jacoby, R. L. et al, J. Med. Chem., 17, 453-455, (1974)). Alkylation of the cyanoacetates of general formula 23, which are commercially available or may be prepared from literature procedures, with alkyl dihalides such as 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yields the chloride 24. Reduction of the nitriles 24 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol to give compounds of structure 20.

SCHEME 27



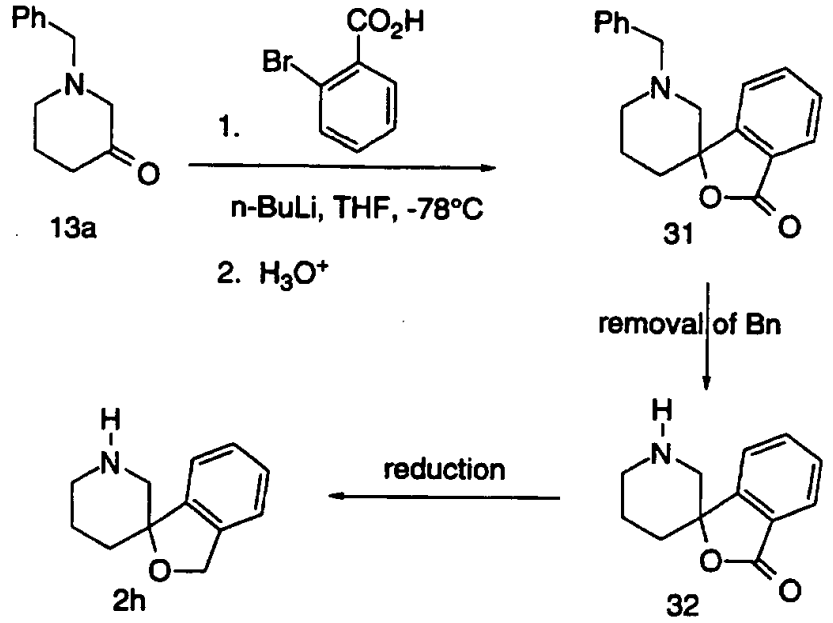
Alternatively, the cyanoacetates of general formula 23 may be alkylated with an ethoxycarbonylalkyl bromide or reacted with ethyl acrylate to give compounds of Formula 26. Reduction of the nitriles 26 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 27. Reduction of the lactam 27 by borane followed by N-protection gives compounds of formula 20 as shown in Scheme 27.

SCHEME 28



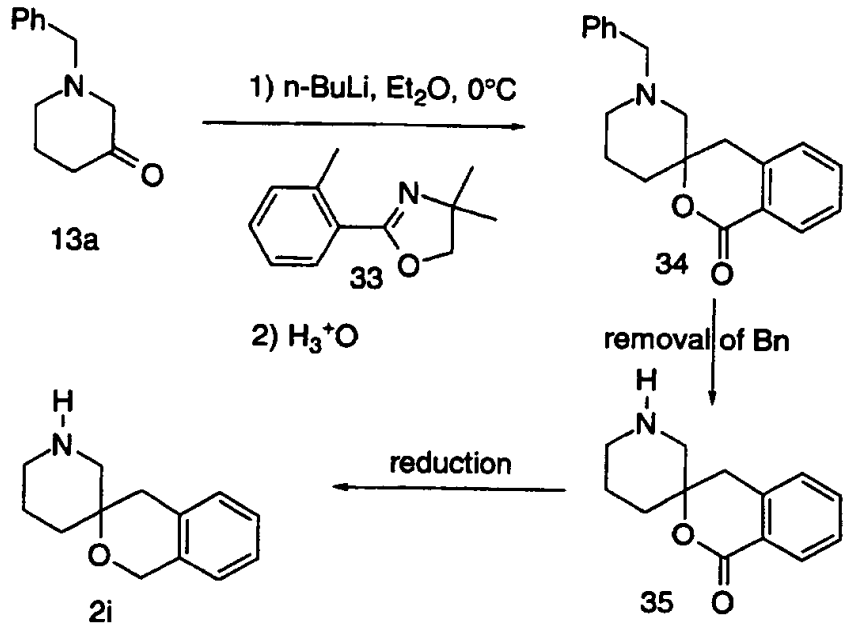
Alternatively, as depicted in Scheme 28 a malonate of general formula 28 may be alkylated with cyanoalkyl bromide or can be reacted with acrylonitrile to form compounds of formula 29. Reduction of the nitriles 29 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 30. Reduction of the lactam 30 by borane followed by N-protection gives compounds of formula 20.

SCHEME 29



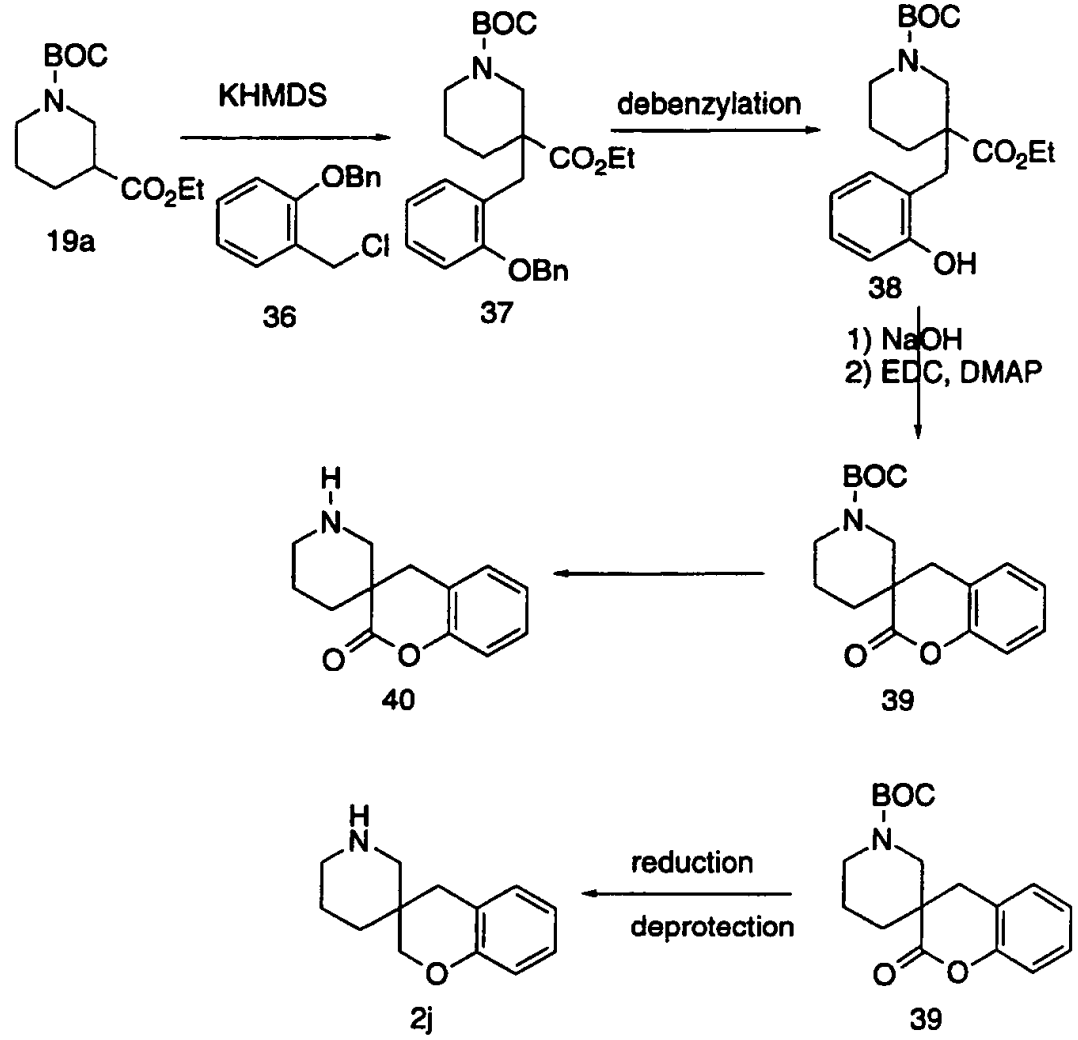
The spiro benzofuran 2h may be prepared by the method originally described by Parham and coworkers (*J. Org. Chem.* 1976, *41*, 2628). Addition of the appropriately substituted Grignard reagent or organolithium reagent to the starting ketone 13a as shown in Scheme 29 followed by mild acid treatment gives the 3-spirolactone 31. The removal of the benzyl protecting group may be accomplished by methods known in the art, such as catalytic hydrogenolysis or using chloroethyl chloroformate followed by hydrolysis, to give the spirolactone 32. Reduction of the lactone to a benzofuran can be accomplished by methods in the literature such as that described by Nakao et al (*J. Org. Chem.* 1972, *37*, 76). and by Baldwin et al (*J. Org. Chem.* 1974, *39*, 2470).

SCHEME 30



A method for the synthesis of 3-spiro 2-benzopyrans in the 3-position of a piperidine or pyrrolidine 2i is illustrated in Scheme 30 and has been described by Fu and coworkers (*J. Org. Chem.* 1985, *50,* 1259). Addition of the benzylic anion generated from the oxazoline 33 to the ketone 13a gives an alcohol which is hydrolyzed with a mild acid to give the lactone 34. Removal of the benzyl group and reduction of the resulting lactone to a 2-benzopyran are accomplished by methods as described above to give the compound 2i.

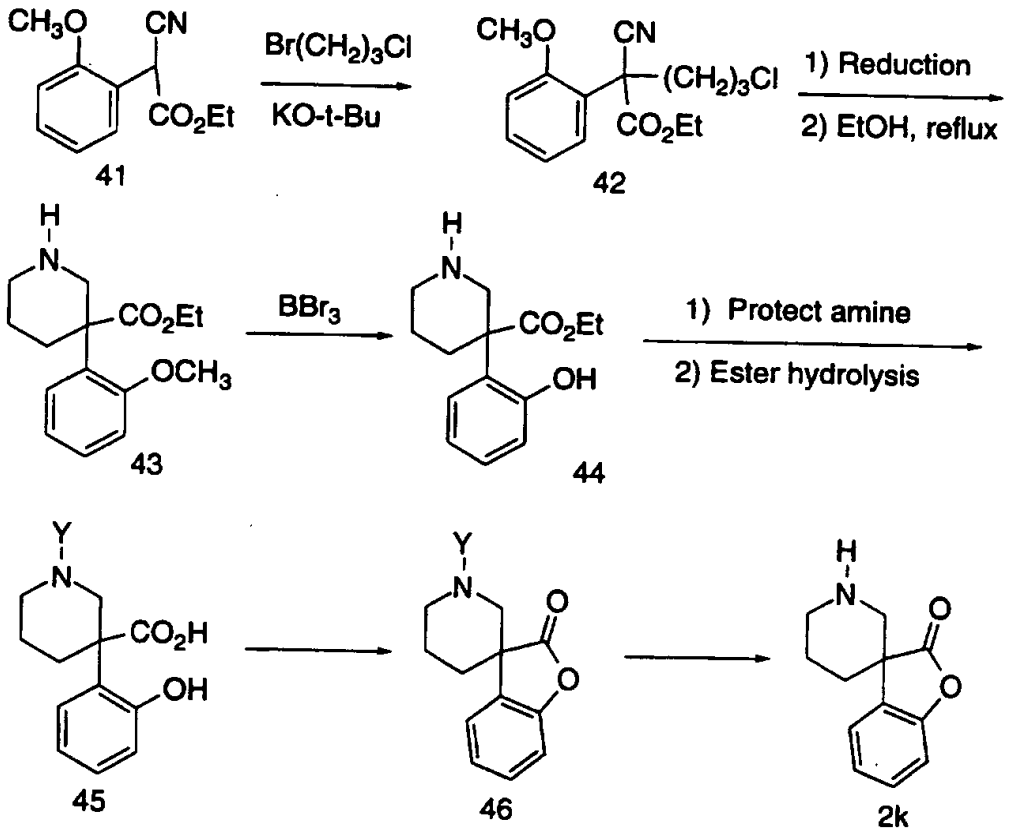
SCHEME 31



The synthesis of piperidines or pyrrolidines with a 3-spirobenzopyran 2j is illustrated in Scheme 31. Alkylation of the appropriately protected ethyl nipecotate such as 19a with the appropriately substituted alkylating reagent such as o-benzyloxy-benzyl chloride 36 gives the compound 37. Removal of the benzyl protecting group by hydrogenolysis gives the phenol 38. Hydrolysis of the ester on 38 followed by lactonization by methods known in the art including that involving activation using EDC/DMAP yield the

lactone 39. and removal of the nitrogen protecting group as described above gives the 3-spirolactone 40. Removal of the Boc group and reduction of the resulting lactone to 2-benzopyran are accomplished by methods as described above to give the compound 2j.

SCHEME 32



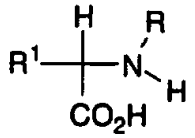
The preparation of piperidines and pyrrolidines with a 3-spirobenzofuran is described in Scheme 32 (see Jacoby et. al., *J. Med. Chem.* 1981, *24*, 218). Ethyl 5-chloro-2-cyano-2-(o-methoxyphenyl)-valerate 41 is alkylated with 1-bromo-3-chloropropane and potassium t-butoxide to give the nitrile 42. The nitrile is reduced to the amine by methods known in the art. The chloride is displaced by refluxing in ethanol or any other high boiling solvent to give the piperidine to afford compound 43. The methyl group is removed by treatment with boron

tribromide to give the indicated phenol. Following protection of the amine (if necessary, for example with a BOC protecting group) by methods known in the art, the ethyl ester is hydrolyzed to give the carboxylic acid 45. The acid is lactonized by methods as described above to give the lactone. Removal of the Boc group and reduction of the resulting lactone to a 2-benzopyran are accomplished by methods as described above to give the compound 2k.

Compounds of the general formula 2 prepared in this way are racemic. Resolution of the two enatiomers can be conveniently achieved by classical crystallization methods by using a chiral acid such as L- or D-tartaric acid, or (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine 2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis.

In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone® in an solvent such as dichloromethane, alcohol or water or their mixtures.

The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formula 28. The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "*Synthesis of Optically Active α-Amino Acids*" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



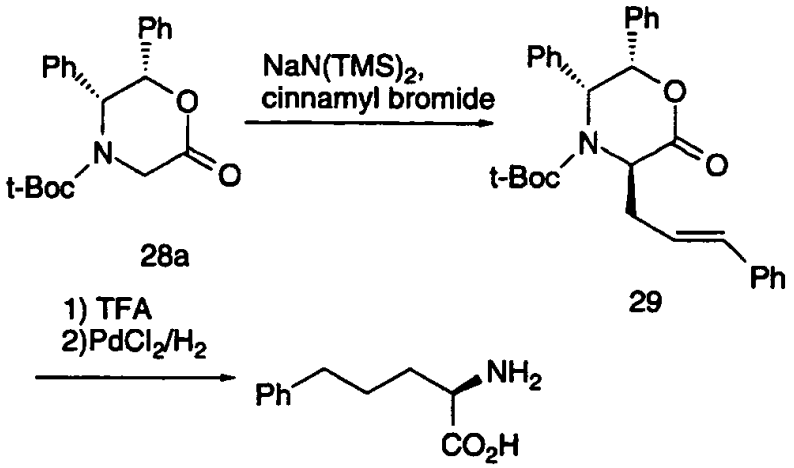
28

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from

optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, *17*, 176).

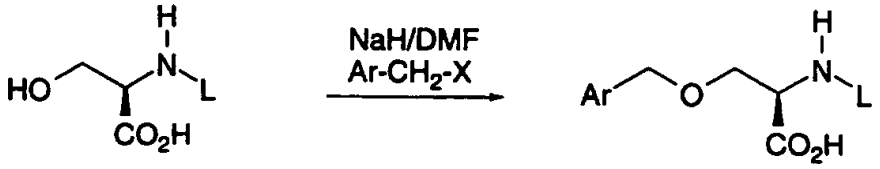
SCHEME 33



28a 29 30

For example, alkylation of the enolate of diphenyloxazinone 28a (*J. Am. Chem. Soc.* 1991, 113, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 29 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 30 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 33).

SCHEME 34



31 32

Intermediates of formula 32 which are O-benzyl-(D)-serine derivatives are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 31. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of 31 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent

such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* 1989, 36) as shown in Scheme 34.

The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula 32 include the acid catalyzed benzylation of carboxyl protected intermediates derived from 31 with reagents of formula Ar-$CH_2OC(=NH)CCl_3$ (O. Yonemitsu et al., *Chem. Pharm. Bull.* 1988, 36, 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* 1991, *113*, 9276; *J. Org. Chem.* 1989, *54*, 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 32. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

It is noted that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, *et al.*, *Science*, *260*, 1640-1643 (1993) (see text of Figure 2 therein). In particular, the intrinsic growth horomone secretagogue activities of the compounds of the present invention may be demonstrated by this assay. The compounds of the following examples have activity in the aforementioned assay in the range of 0.1 nm to 5 μm.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release and that the growth hormone releasing factor (GRF) stimulates its release. Other hormones that are important and in need of study as to

their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the

catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, amino acids, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the compounds of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α-adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. In particular, the compounds of this invention may be used in combination with growth hormone releasing factor, an analog of growth hormone releasing factor, IGF-1, or IGF-2. For example, a compound of the present invention may be used in combination with IGF-1 for the treatment or prevention of obesity. In addition, a compound of this invention may be employed in conjunction with retinoic acid to improve the condition of musculature and skin that results from intrinsic aging.

The present invention is further directed to a method for the manufacture of a medicament for stimulating the release of growth hormone in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same

effects or uses as growth hormone itself. These varied uses may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treating obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia; treatment of hypercortisonism and Cushing's syndrome; treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development and preventtion of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; treatment of syndromes manifested by non-restorative sleep and

musculoskeletal pain, including fibromyalgia syndrome or chronic fatigue syndrome; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock. Likewise, the instant compounds are useful in a method of treatment of diseases or conditions which are benefited by the anabolic effects of enhanced growth hormone levels that comprises the administration of an instant compound.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

In addition, the instant compounds may be useful in the treatment of illnesses induced or facilitated by corticotropin releasing factor or stress- and anxiety-related disorders, including stress-induced depression and headache, abdominal bowel syndrome, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional,

complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., "Role of Bisphosphonates in Metabolic Bone Diseases" *Trends in Endocrinol. Metab.*, *4*, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

In the case of alendronate daily oral dosage levels of 0.1 mg to 50 mg are combined for effective osteoporosis therapy with 0.01 mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention.

Osteoporosis and other bone disorders may also be treated with compounds of this invention in combination with calcitonin, estrogens, raloxifene and calcium supplements such as calcium citrate or calcium carbonate.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltesterone, fluoxymesterone and stanozolol.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or

topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

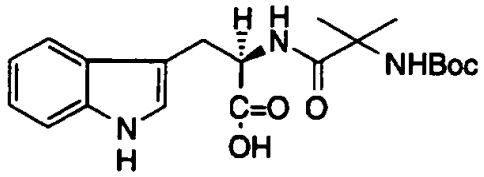
Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

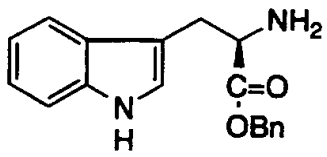
The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone. Preferably, the dosage level will be about 0.001 to about 25 mg/kg per day; more preferably about 0.01 to about 10 mg/kg per day.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

INTERMEDIATE 1



Step A:

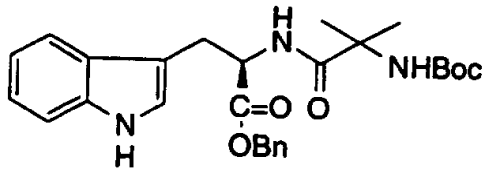


To a solution of the commercially available N-t-BOC-D-tryptophan (25.0 g, 82.2 mmol), benzyl alcohol (10.2 mL, 98.6 mmol), and DMAP (100 mg) in dichloromethane (200 mL) at 0°C, was added EDC (17.4 g, 90.4 mmol) in several portions over a one hour period. The reaction mixture was stirred at room temperature for six hours and was poured into water (200 mL), and the organic layer was separated. The

organic solution was washed with a mixture of brine and 3 N hydrochloric acid, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which solidified upon standing.

To a solution of this oil in 30 mL of dichloromethane was added 20 mL of TFA and stirred for 1h. The reaction mixture was concentrated, neutralized carefully with saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane (2X100 mL). The combined organic solution was washed with brine (100 mL), passed through a short column of silica gel eluting with 5-10% methanol in dichloromethane to give 23.2 g of the amine as an oil after evaporation.

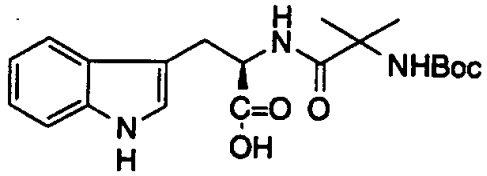
Step B:



To a solution of the above product , HOBT (10.6 g, 78.8 mmol) and N-BOC-α-methyl alanine (19g, 94.5 mmol) in 200 mL of dichloromethane, was added EDC (19.5 g, 0.102 mol) in several portions at 0°C. After 5 minutes, the clear reaction mixture became milky. After stirring at room temperature overnight, the reaction mixture was poured into 200 mL of water and the organic layer was separated. The organic solution was washed with brine, and with a brine and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which was purified by flash chromatography eluting with 10-40% ethyl acetate in hexane to give the desired material (28.7 g).

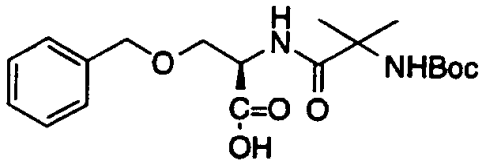
^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.48 (br.s, 1H), 7.54 (br.d, 1H), 7.38-7.23 (m, 3H), 7.19 (br.d, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (br.s, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

Step C:



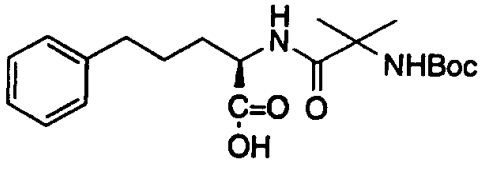
A solution of the material from Step B (28.7g) in 200 mL of ethanol was stirred at RT under a H_2 balloon for 20 minutes in the presence of 10% palladium on carbon (2 g). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a slightly pink foam (23.3 g).
^{1}H NMR (CD_3OD, 400 MHz) δ 7.56 (d, J=8 Hz, 1 H), 7.31 (dd, J=1, 8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (dt, J=1, 7 Hz, 1 H), 6.98 (dt, J=1, 7 Hz, 1 H), 4.69 (t, J=6 Hz, 1 H), 3.34-3.23 (m, 2 H), 1.35 (s, 3 H), 1.34 (s, 9 H), 1.29 (s, 3 H).
FAB-MS calc. for $C_{20}H_{27}N_3O_5$: 389 ; Found 390 (M+H), 290 (M+H-100 (BOC))

INTERMEDIATE 2



Following the procedures for the preparation of Intermediate 1 using N-t-Boc-O-Benzyl-D-serine in the place of N-t-BOC-D-tryptophan gave Intermediate 2. FAB-MS calc. for $C_{19}H_{28}N_2O_6$: 380; Found 381 (M+H), 325 (M+H-56 (t-Bu)), 281 (M+H-100 (BOC)).

INTERMEDIATE 3



Step A: (DL)-N-Acetyl-2-amino-5-phenylpentanoic acid

To a solution of sodium (2.3 g, 0.1 mol) in ethanol (60 mL) under nitrogen at room temperature, was added diethyl acetamidomalonate. The mixture was stirred at room temperature for one hour, and then 1-bromo-3-phenylpropane was added dropwisely. After the addition, the mixture was stirred at room temperature for two hours, then refluxed overnight. It was cooled to room temperature and partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate in water, dried over MgSO4 and evaporated to give an intermediate (32.5 g, 97%).

^{1}H NMR (CDCl3, 400MHz) 7.26-7.10 (m, 5 H); 6.75 (br. s, 1 H); 4.19 (q, J=7 Hz, 4 H); 2.58 (t, J=7.9 Hz, 2 H); 2.39-2.35 (m, 2 H); 2.00 (s, 3 H); 1.43-1.39 (m, 2 H); 1.20 (t, J=7 Hz, 6 H).

The product above was suspended in 190 mL of 2.5 N NaOH in water and refluxed for two hours. The mixture was cooled to 0°C, and it was carefully neutralized with 6 N HCl to pH2. The precipitate was collected using a glass sinter funnel and washed with a small amount of cold water and air dried. The solid was then suspended in 300 mL of water and refluxed for four hours. The solution was cooled and acidified to pH1 and the solid was collected by filtration (15.3 g, 67%).

^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step B: (D)-N-Acetyl-2-amino-5-phenylpentanoic acid

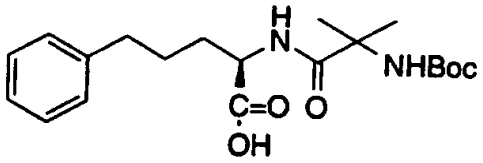
The racemic intermediate from the previous step (10 g, 42.5 mmol) and CoCl3-6H2O were dissolved in 21 ml of 2 N KOH and 200 mL of water at 40°C, and the pH of the solution was adjusted to 8 by the addition of the several drops of 2 N KOH. Then acylase I (Aspergillus sp, 0.5 u/mg, from Sigma; 0.9 g) was added with vigorous stirring. The reaction mixture was stirred for one day at 40°C and the pH was kept at 8 by the addition of a few drops of KOH. The solid which formed was filtered off. The filtrate was acidified by 3 N HCl to pH2, and was

extracted with ethyl acetate (200 mLX4). The organic extracts were combined and evaporated to give a white solid (4.64 g, 46%) ^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step C: (D)-N-t-Boc-2-amino-5-phenylpentanoic acid

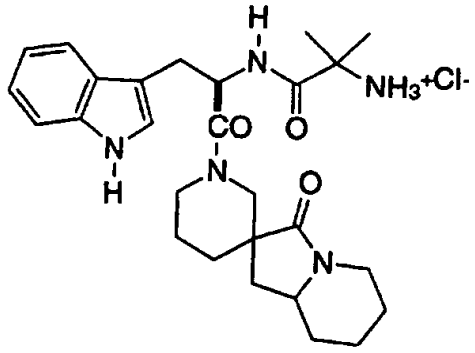
The intermediate from step B (4.2 g, 17.8 mmol) was suspended in 2 N HCl (100 mL) and refluxed for two hours. The reaction mixture was evaporated in vacuo to remove water and hydrochloric acid to yield a white solid. To a solution of this solid in 50 mL of water, was added 3 N NaOH until the pH 11, then di-t-butyl dicarbonate (4.66 g, 21.4 mmol) was added with vigorous stirring. After four hours, the reaction mixture was acidified to pH2 with 3 N HCl and it was extracted with ethyl acetate (100 mLX3). The organic extracts were combined and evaporated to give a white solid (6.56 g, crude) which was used without purification. ^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.11-4.08 (m, 1 H); 2.65-2.60 (m, 2 H); 1.83-1.62 (m, 4 H); 1.43 (s, 9 H).

Step D:

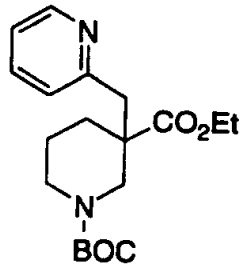


Following the procedures for the preparation of Intermediate 1 using (D)-N-t-Boc-2-amino-5-phenylpentanoic acid in the place of N-t-BOC-D-tryptophan gave Intermediate 3. ^{1}H NMR ($CDCl_3$, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

EXAMPLE A1



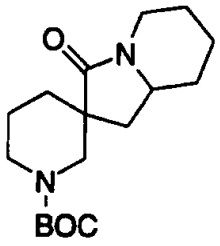
Step A:



To a stirred solution of ethyl N-t-Boc nipecotate (50 g, 0.196 mol) in THF (600 mL) at -78°C under argon was added KHMDS (0.5 M in toluene, 298 mL, 0.298 mol) over a 30 minute period. The solution was allowed to stir an additional 30 minutes at -78°C. Meanwhile, a suspension of 2-picolyl chloride hydrochloride (25 g) in dichloromethane was washed with a mixture of 3 N NaOH and brine to remove the hydrochloride. The organic layer was dried over $MgSO_4$ and evaporated to yield a brown oil and it was added slowly to the solution at -78°C. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography eluting with a solvent gradient of 20-80% ethyl acetate in hexane provided the title compound. (54.8 g, 80%). ^1H NMR (CD_3OD, 400MHz) d 8.45 (dd, J = 1.5 Hz, 5 Hz, 1 H),

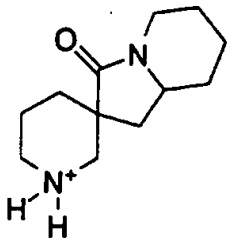
7.52 (app dt, J = 2 Hz, 8 Hz, 1 H), 7.07 (dd, J = 5 Hz, 6.6 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 4.09-4.04 (br. m, 2 H), 3.92 (br. d, 1 H), 3.46 (br. m, 1 H), 3.30-3.10 (br. m, 1 H), 3.06 (d, J = 13.7 Hz, 1 H), 2.95 (d, J = 13. 7 Hz, 1 H), 2.01-1.91 (br. m, 1 H), 1.63-1.50 (br. m, 3 H), 1.36 (v. br. s, 9 H), 1.13 (t, 7.1 Hz, 3 H). FAB-MS calc. for $C_{19}H_{28}N_2O_4$: 348; Found 349 (M+H).

Step B:



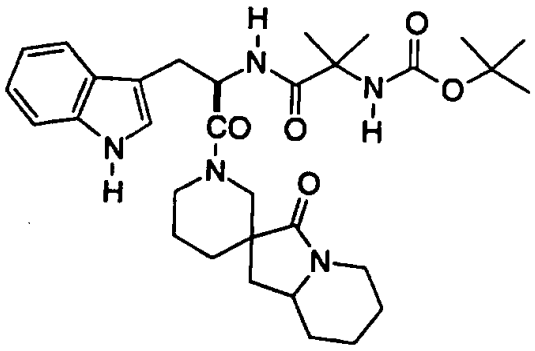
A suspension of PtO_2 (250 mg) and the intermediate from the previous step (5 g) in ethanol (20 mL) and acetic acid (2 mL) was vigorously stirred under a hydrogen atmosphere overnight. The reaction mixture was then filtered through celite and evaporated to give a residue, which was refluxed in ethanol overnight. Evaporation and purification by SiO2 flash column chromatography gave the desired two diastereomers. The compound which came out first from the column was designated as d1 (1.95g); and the compound which came out of the column second was designated as d2 (1.97 g), (d1: 1.95 g; d2: 1.97 g). FAB-MS calc. for $C_{17}H_{28}N_2O_3$: 308; Found 309 (M+H)

Step C:



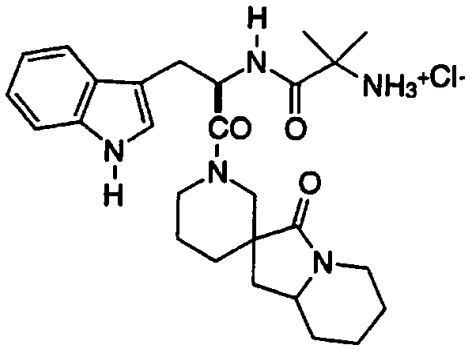
A solution of the intermediates from the previous step each (d1: 1.95 g; d2: 1.98 g) in ethyl acetate (5mL each) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (d1: 1.49 g; d2: 1.52g). ESI-MS calc. for $C_{12}H_{20}N_2O$: 208; Found 209 (M+H)

Step D:



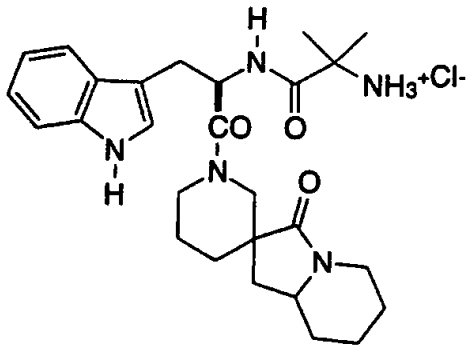
To a solution of the intermediate (d1) prepared in the previous step (189 mg), intermediate 1 (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with ethyl acetate provided the product as a diastereomeric mixture (384 mg).
ESI-MS calc. for $C_{32}H_{45}N_5O_5$: 579; Found 580 (M+H)

Step E:



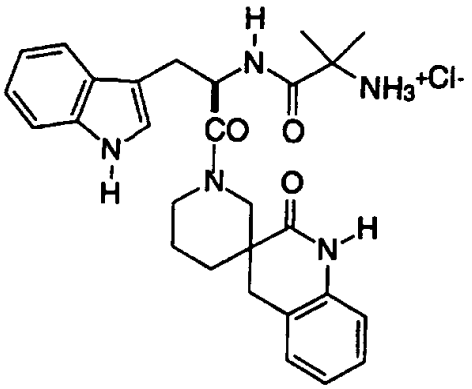
A solution of the intermediates from the previous step each (384 mg) in ethyl acetate (5mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (330 mg). ESI-MS calc. for $C_{27}H_{37}N_5O_3$: 479; Found 480 (M+H)

Step F:

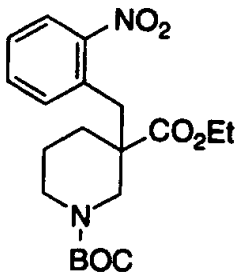


The title compound was prepared similarly from the intermediate d2 from Step C, Example A1 as described by steps D and E. ESI-MS calc. for $C_{27}H_{37}N_5O_3$: 479; Found 480 (M+H)

EXAMPLE A2

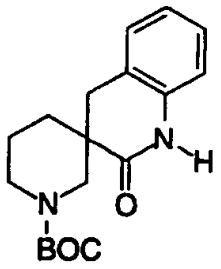


Step A:



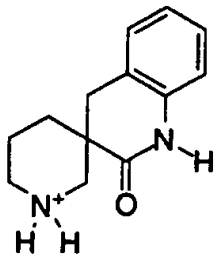
To a -78°C solution of the N-BOC ethyl nipcotate (1.5 g, 5.83 mmol) in THF was added LHMDS (8.74 mL of a 1M solution in THF, 8.74 mmol). The reaction was allowed to warm to 0°C over 0.5 h then recooled to -78°C whereupon a solution of 2-nitrobenzyl bromide (1.51 g, 6.99 mmol) in THF (5 mL) was added dropwise. The reaction was then allowed to warm to room temperature. The reaction mxture was then partitioned between EtOAc and saturated ammonium chloride. The organic layer was washed with water, brine and dried ($MgSO_4$). The mixture was filtered, concentrated and the residue was chromatographed (4:1 hexanes:EtOAc)to give 0.5 g of the title compound: MS (CI) 293.2 (M-100+H), 202.1.

Step B:



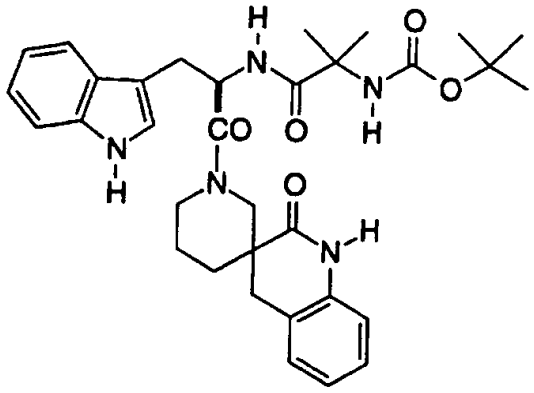
To a solution of the nitro compound (500 mg) in methanol (25 mL) was added 10% Pd/C (30% wt) and a balloon of hydrogen gas was affixed. The reaction was maintained at room temperature for 2 hours whereupon it was filtered and concentrated in vacuo to provide 0.21g of the title compound: MS (CI) 217.2 (M-100+H).

Step C:



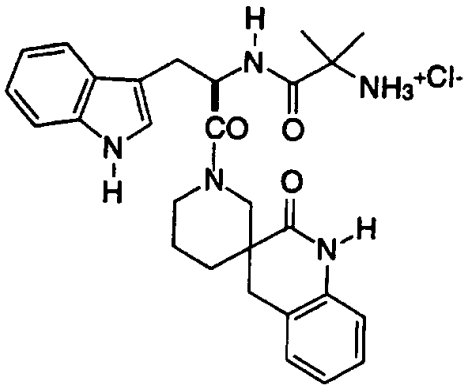
A solution of the intermediate from the previous step (34 mg) in ethyl acetate (1 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (25 mg).
ESI-MS calc. for $C_{13}H_{16}N_2O_2$: 216; Found 217 (M+H)

Step D:



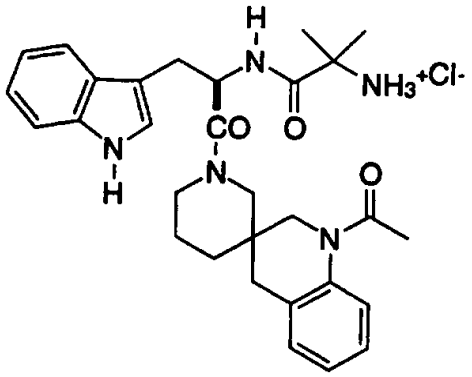
To a solution of the intermediate prepared in the previous step (23 mg), intermediate 1 (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 80% ethyl acetate in hexane provided the product as a diastereomeric mixture (28 mg).
ESI-MS calc. for $C_{33}H_{41}N_5O_5$: 587; Found 588 (M+H)

Step E:

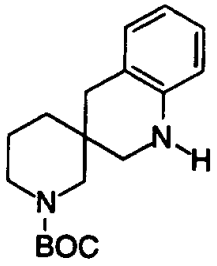


A solution of the intermediates from the previous step each (28 mg) in ethyl acetate (1mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (19 mg). ESI-MS calc. for $C_{28}H_{33}N_5O_3$: 487; Found 488 (M+H)

EXAMPLE A3



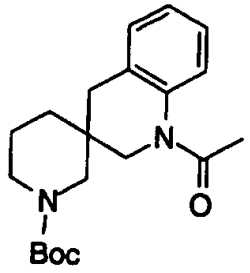
Step A:



To a solution of the lactam (100 mg, 0.315 mmol) in THF (4 mL) at 0°C was added a 1 M solution of BH_3-THF (1 mL, 1 mmol). The reaction was refluxed three hours until complete by HPLC analysis. The reaction was partitioned between ethyl acetate and $NaHCO_3$ (sat'd), washed with water, brine and dried (Na_2SO_4). The solvent was removed

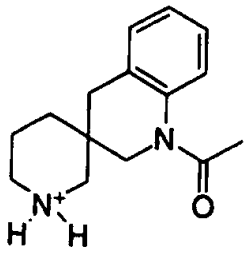
invacuo to provide 90 mg of the title compound: MS(CI) 304.2 (M+H), 204.2.

Step B:



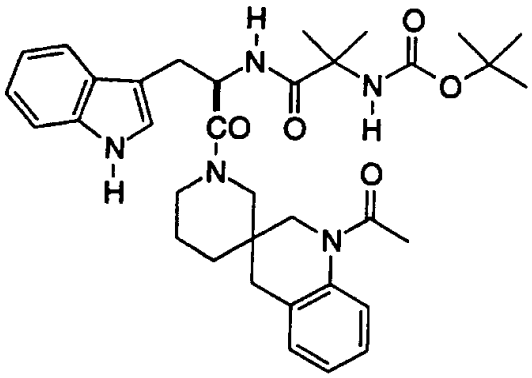
To a solution of the amine (72 mg, 0.237 mmol) in CH2Cl2 (16 mL) was added TEA (100 mL, 0.71 mmol), DMAP (catalytic amount) and lastly the acetic anhydride (45 mL, 0.48 mmol). The solution was stirred until complete by TLC analysis. The reaction was partitioned between ethyl acetate and $NaHCO_3$ (sat'd), washed with water, brine and dried (Na_2SO_4). The solution was concentrated and the residue chromatographed to afford 60 mg of the title compound: MS(ESI) 345.1 (M+H), 302.1, 245.1.

Step C:



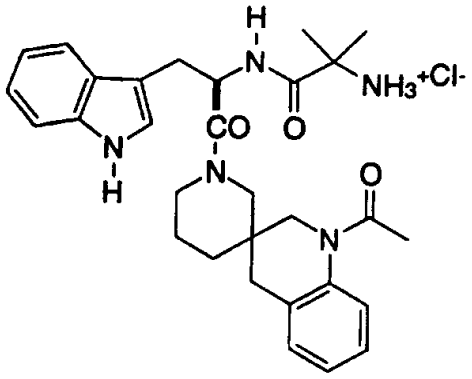
The N-BOC group was removed as described above with HCl/EtOAc to provide the title compound: ^{1}HNMR (400 MHz, $CDCl_3$) 2H, dd, 2.79.

Step D:



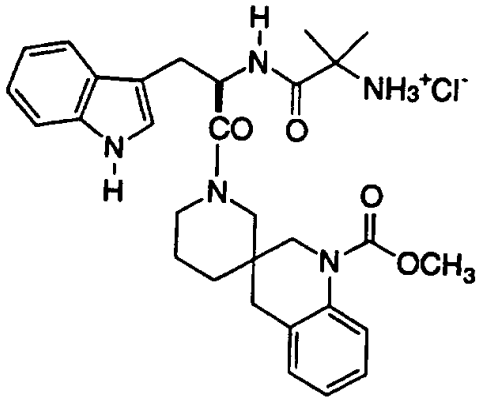
To a solution of the amine salt (22 mg, 0.90 mmol) in CH_2Cl_2 (2.2 mL) was added the d-Trp-N-BOC acid (35 mg, 0.09 mmol), EDCI (35 mg, 0.18 mmol) and HOBt (12 mg, 0.90 mmol). The reaction was allowed to stir until complete by TLC analysis. Workup and chromatography gave 38 mg of the title compound as a mixture of diastereomers which were not separated: MS (ESI) 616.1 (M+H), 516.1, 245.0.

Step E:

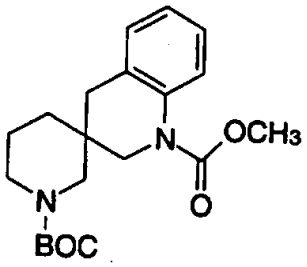


The N-BOC group was removed as described above with HCl/EtOAc to provide the title compound as a mixture of diastereomers: MS (ESI) 516.1 (M+H).

EXAMPLE A4

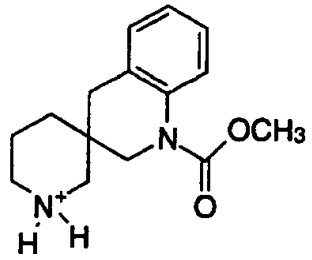


Step A:



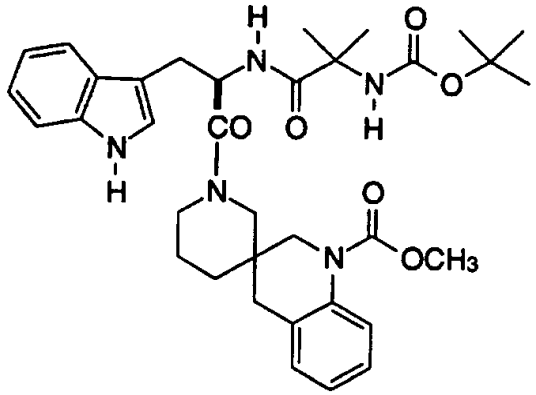
To a solution of the amine (43 mg, 0.14 mmol) in methyl ethyl ketone (2.5 mL) was suspended K_2CO_3 (22 mg, 0.156 mmol) and the methyl chloroformate (17.6mL, 0.213 mmol) was added. The reaction mixture was stirred at 50°C until complete by TLC analysis. The reaction was partitioned between ethyl acetate and $NaHCO_3$ (sat'd), washed with water, brine and dried (Na_2SO_4). The solvent was removed in vacuo to provide 38 mg of the title compound: ^{1}HNMR (400 MHz, $CDCl_3$) 2H, dd, 2.59.

Step B:



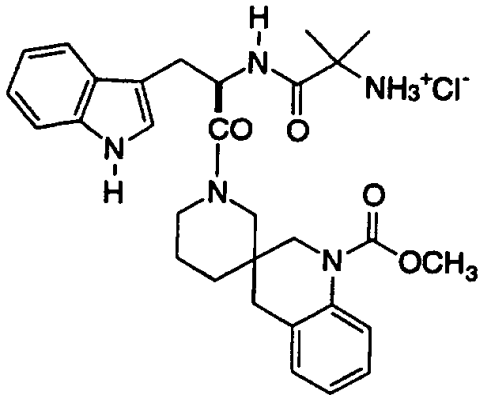
The N-BOC group was removed as described above with HCl/EtOAc to provide the title compound as a mixture of diastereomers: MS (ESI) 261.2 (M+H), 199.2.

Step C:



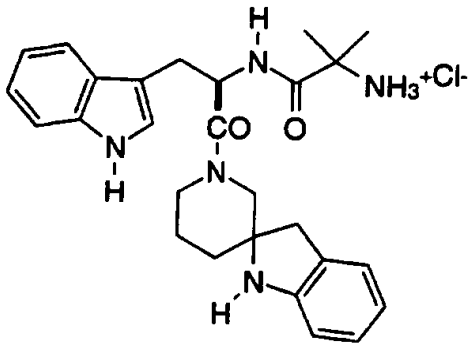
To a solution of the amine salt (35 mg, 0.11 mmol) in CH_2Cl_2 (2.2 mL) was added the d-Trp-N-BOC acid (42 mg, 0.11 mmol), EDCI (41 mg, 0.22 mmol) and HOBt (15 mg, 0.11 mmol). The reaction was allowed to stir until complete by TLC analysis. Workup and chromatography gave 75 mg of the title compound as a mixture of diastereomers which were not separated: MS (ESI) 632.2 (M+H), 532.2, 261.0.

Step D:

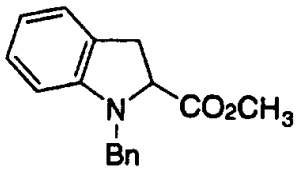


The N-BOC group was removed as described above with HCl/EtOAc to provide the title compound as a mixture of diastereomers: MS (ESI) 532.2 (M+H), 475.2.

EXAMPLE A5

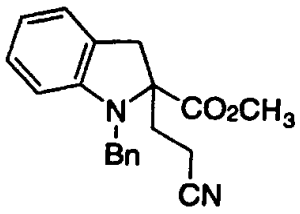


Step A:



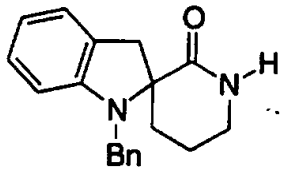
To a solution of the methyl ester (31 g, 0.17 mol) in dry methanol (250 mL) was added K_2CO_3 (46.9 g, 0.17 mol) and benzyl bromide (31.0 mL, 0.26 mmol) and the reaction was heated to reflux until complete by TLC analysis. The reaction was then filtered and concentrated in vacuo. The residue was dissolved in ether and the ether layer was washed with 2N HCl (3x100 mL). Tha combined aqueous layers were made basic with 5N NaOH and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (K_2CO_3) and concentrated. Chromatography of the residue (4:1 hexanes:ethyl acetate) gave 14.3 g of the title compound: MS(CI) (M+H).

Step B:



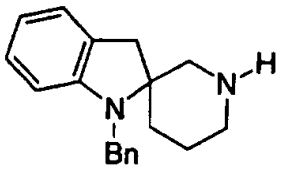
To a -78°C solution of LDA (generated from 3.15 mL, 22.4 mmol of diisopropyl amine and 8.97mL of a 2.5M solution of n-BuLi in 45 mL of THF) was added the methyl ester (4.0 g, 14.96 mmol) in THF (2x10 mL) dropwise. The mixture was maintained at -78°C for 1 hour whereupon 3-bromo proprionitrile (3.7 mL, 44.8 mmol) was added dropwise. The rection was warmed to room temperature and stirred for 1 hour. The reaction was then quenched with saturated ammonium chloride and the extracted with ethyl acetate. The ethyl acetate layers were washed with water, brine, dried (Na2SO4) and concentrated. Chromatography of the residue (5:1 hexanes:ethyl acetate) gave 2.19 g of the title compound: MS(CI) 321.1 (M+H).

Step C:



To a solution of the nitrile (2.19 g, 6.86 mmol) in refulxing THF (20 mL) was added borane dimethyl sulphide (10.3 mL, 20.6 mL) dropwise. The reaction was maintained at reflux for 40 minutes whereupon it was cooled to room temperature and 6N HCl (10 mL) was added very cautiously. The reaction was then heated to reflux for 30 minutes then cooled to room temperature and 5N NaOH was added so that the pH=11. The reaction was then diluted with ethyl acetate and washed with water, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in methanol (10 mL) and sodium methoxide was added. The reaction was stirred overnight at room temperature. The following morning the reaction was concentrated and the residue was dissolved in ethyl acetate and washed with water, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue (1:1 hexanes:ethyl acetate) gave 0.70 g of the title compound: MS(CI) 291.1, 272.0, 261.1, 259.1, 258.1, 234.1.

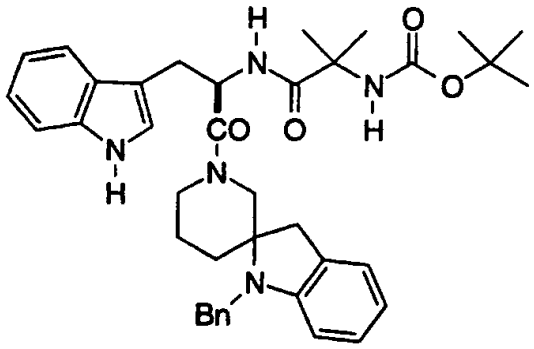
Step D:



To a solution of the amide (34 mg, 0.12 mmol) in THF (1 mL) was added borane tetrahydrofuran (0.58 mL, 0.58 mmoL) dropwise. The reaction was maintained at reflux for 2 hours whereupon it was cooled to room temperature and 6N HCl (5 mL) was added very cautiously. The reaction was then heated to reflux for 30 minutes then

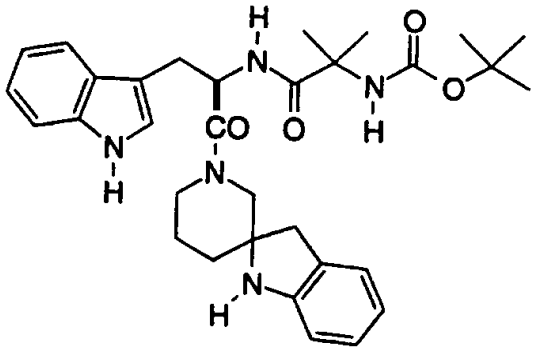
cooled to room temperature and 5N NaOH was added so that the pH=11. The reaction was then diluted with ethyl acetate and washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue (10:1 CH_2Cl_2:CH_3OH) gave 17.5 mg of the title compound: MS(CI) 279.2 (M+H), 259.1, 234.1.

Step E:



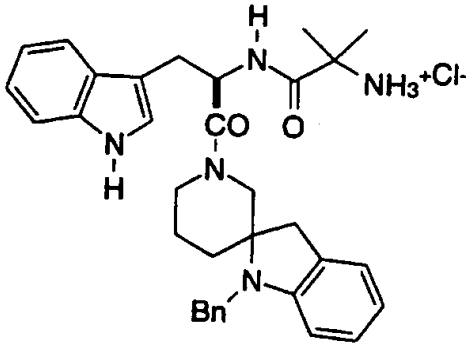
To a solution of the 3-spiroamine (100 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added EDCI (137 mg, 0.72 mmol), HOBt (48.5 mg, 0.36 mmol) and the d-Trp-N-BOC-AIB carboxylic acid (139 mg, 0.36 mmol). The reaction was maintained at room temperature until complete by TLC whereupon it was diluted with etyl acetate, washed with 2N HCl, sat. $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue (2:1 ethyl acetate:hexanaes) gave 102 mg of the title compound as a mixture of diastereomers: MS(CI) 650.2(M+H), 594.2, 550.2, 511.1, 279.1.

Step F:



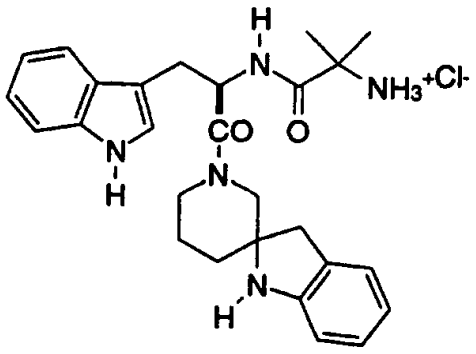
To a solution of the N-benzyl amine (35 mg) in methanol (2 mL) was added 10% Pd/C (50 mg) and the reaction was maintained under an atmosphere of hydrogen overnight. The following morning the reaction was filtered through celite with CH_2Cl_2. The filtrate was concentrated to give 21.5 mg of the title compound: MS(CI) 560.2 (M+H), 504.1, 460.3, 375.0.

Step G:



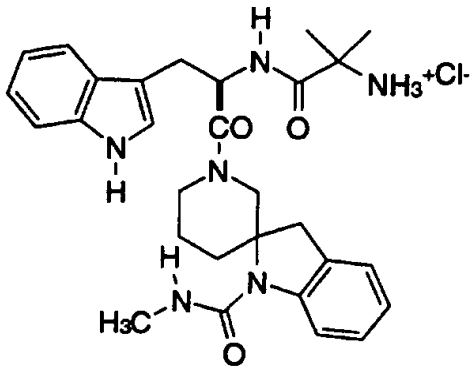
The N-BOC compound was deprotected as described above with HCl/EtOAC to give the title compound.

Step H:

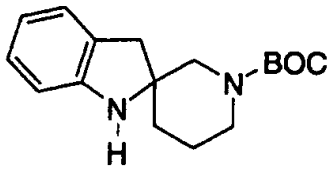


The N-BOC compound was deprotected as described above with HCl/EtOAC to give 20 mg of the title compound.

EXAMPLE A6



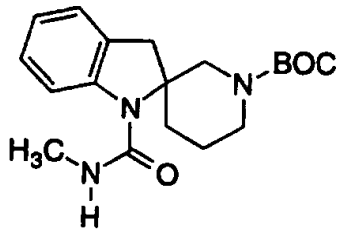
Step A:



To a solution of the amine (440 mg, 1.58 mmol) in CH_2Cl_2 (10 mL) was added triethyl amine (0.33 mL, 2.4 mmol) and BOC anhydride (379 mg, 1.73 mmol). The reaction was stirred 20 minutes,

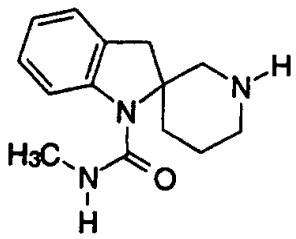
diluted with CH_2Cl_2 and washed with sat. NH_4Cl and brine. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in methanol (10 mL) to which was added 10% Pd/C. The mixture was stirred rapidly under an atmosphere of hydrogen until the reaction was complete as indicated by TLC analysis. The reaction was then filtered through a pad of celite with CH_2Cl_2. The filtrate was concentrated and the residue was chromatographed (4:1 hexanes:ethyl acetate) to give 270 mg of the title compound.

Step B:



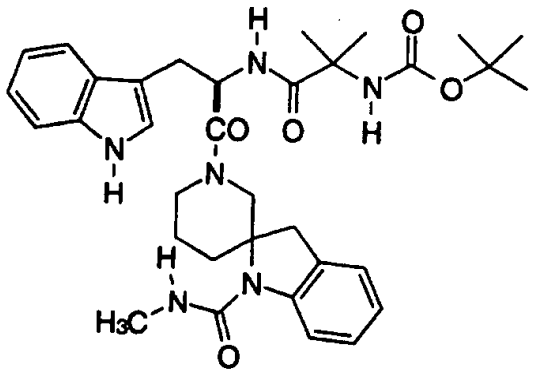
To a solution of the aniline (150 mg, 0.52 mmol) in CH2Cl2 (5.0 mL) was added triethyl, amine (1.45 mL, 10.4 mmol) and methyl isocyanate (0.31 mL, 5.20 mmol). The reaction was heated to reflux until complete as indicated by TLC analysis. The mixture was diluted with CH_2Cl_2 and washed with 2N HCl, sat. $NaHCO_3$, brine and dried (Na_2SO_4). The mixture was filtered and concentrated. Chromatography (2:1 hexanes:ethyl acetate) of the residue gave the title compound: MS(CI) 346.2 (M+H), 290.2, 246.2, 228.2, 215.2.

Step C:



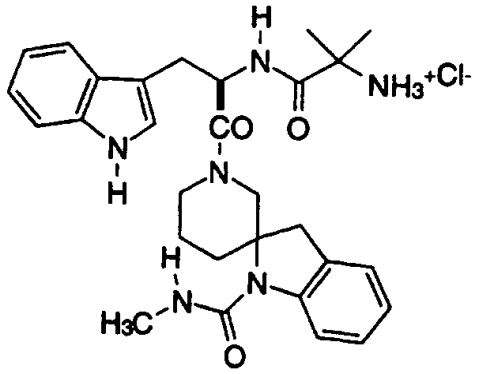
The N-BOC methyl urea (165 mg) was deprotected with HCl/EtOAc as per the standard deprotection protocol. Basic workup gave 124 mg of the free amine: MS(CI) 246.2 (M+H), 189.2.

Step D:



To a solution of the methyl urea (30 mg, 0.12 mmol) in CH_2Cl_2 (3.0 mL) was added EDCI (46.7 mg, 0.24 mmol), HOBt (16.5 mg, 0.12 mmol) and the d-TrpN-BOC-AIB carboxylic acid (45.5 mg, 0.12 mmol). The reaction was maintained at room temperature until complete by TLC whereupon it was diluted with ethyl acetate, washed with 2N HCl, sat. $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated. Radial chromatography (2mm plate; 4:1 ethyl acetate) gave 2 separate diastereomers: D1 (higher Rf) 25.9 mg: MS(ESI) 617.2 (M+H), 561.2, 246.0. : D2 (lower Rf) 27 mg: MS(ESI) 617.3 (M+H), 560.2, 504.2, 420.6, 245.9.

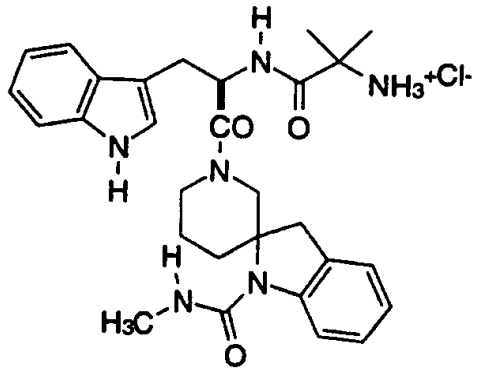
Step E:



Diastereomer #1 (higher Rf)

The N-BOC group was deprotected as described above (HCl/EtOAc) to give the title compound: MS(CI) (M+H).

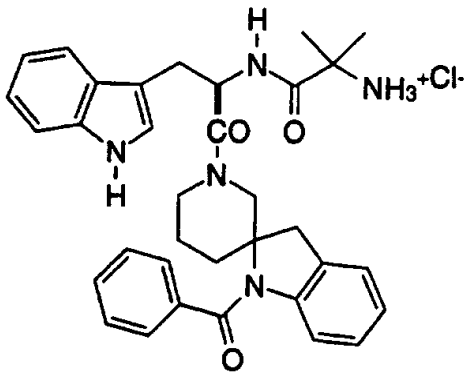
Step F:



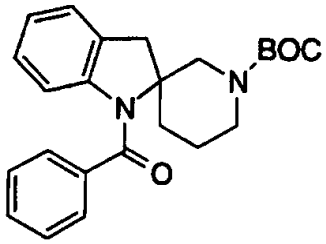
Diastereomer #2 (lower Rf)

The N-BOC group was deprotected as described above (HCl/EtOAc) to give the title compound.

EXAMPLE A7

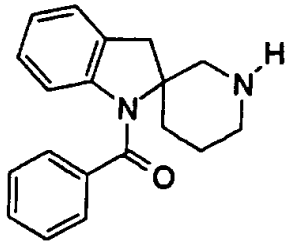


Step A:



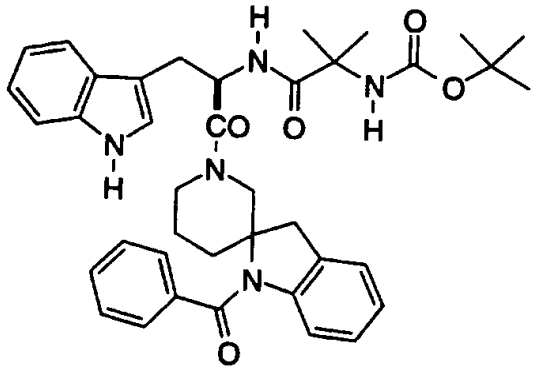
To a 0°C solution of the aniline (100 mg, 0.35 mmol) in THF (1.0 mL) was added n-BuLi (0.21 mL of a 2.5 molar solution, 0.52 mmol). The reaction was stirred for 15 minutes whereupon freshly distilled benzoyl chloride (0.20 mL, 1.73 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for approximately 30 minutes. The reaction was then diluted with ethyl acetate and washed with 2N HCl, brine, dried (Na_2SO_4) and concentrated. Radial chromatography (4 mm plate; 5:1 hexanes:ethyl acetate) gave 105 mg of the title compound: MS(CI) 293.2 (M+H-CO_2t-Bu).

Step B:



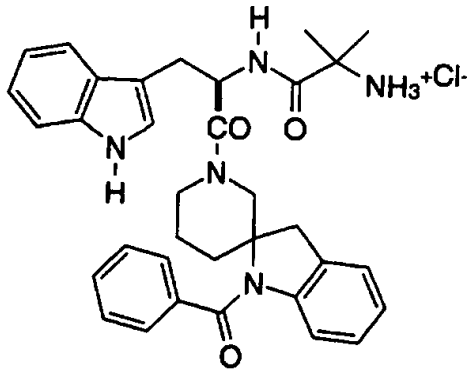
The N-BOC compound (105 mg) was deprotected as described above (HCl/EtOAc). Basic workup gave 92.6 mg of the title compound: MS(CI) 293.2 (M+H).

Step C:



To a solution of the amide (42 mg, 0.14 mmol) in CH_2Cl_2 (3.0 mL) was added EDCI (58.4 mg, 0.29 mmol), HOBt (19.3 mg, 0.14 mmol) and the d-Trp-N-BOC-AIB carboxylic acid (55.9 mg, 0.14 mmol). The reaction was maintained at room temperature until complete by TLC whereupon it was diluted with ethyl acetate, washed with 2N HCl, sat. $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated. Radial chromatography (2 mm plate; 4:1 ethyl acetate) gave 2 separate diastereomers: D1 (higher Rf) 19.0 mg: MS(CI) 664.1 (M+H), 564.1, 293.0: D2 (lower Rf) 27.4 mg: MS(CI) 664.1 (M+H), 564.1, 293.0.

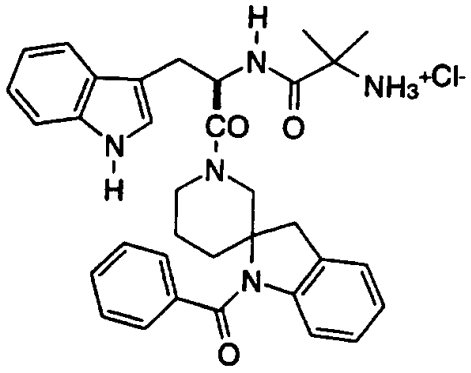
Step D:



Diastereomer #1 (higher Rf)

The N-BOC group was deprotected as described above (HCl/EtOAc) to give the title compound.

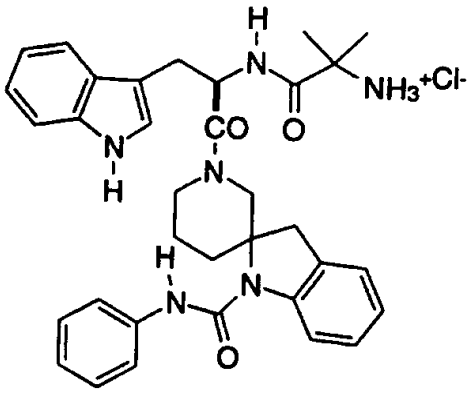
Step E:



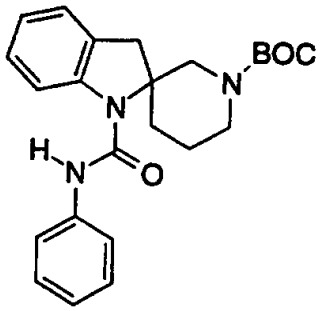
Diastereomer #2 (higher Rf)

The N-BOC group was deprotected as described above (HCl/EtOAc) to give the title compound.

EXAMPLE A8

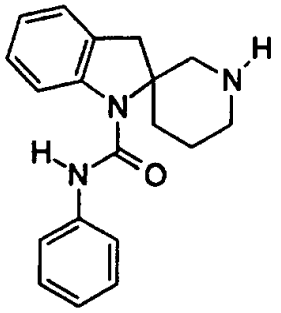


Step A:



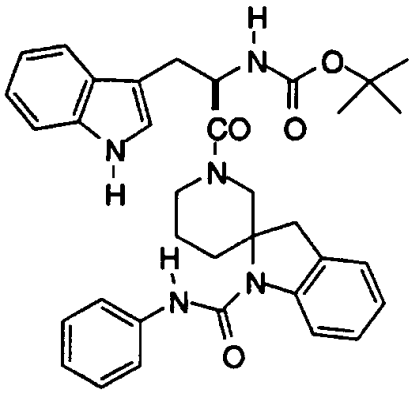
To a solution of the aniline (250 mg, 0.87 mmol) in CH_2Cl_2 was added triethylamine (2.4 mL, 17.3 mmol) and phenyl isocyanate (0.95 mL, 8.7 mmol). The reaction was stirred until complete by TLC analysis whereupon it was diluted with CH_2Cl_2 and washed with 2N HCl, sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Chromatography of the residue gave the title compound: MS (CI) 308.2 (M-100+H).

Step B:



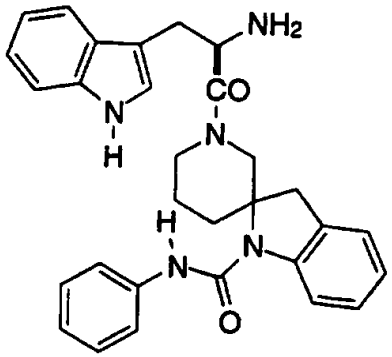
The N-BOC spirocycle was deprotected as described above with TFA to give the title compound: MS (CI) 308.2 (M+H).

Step C:



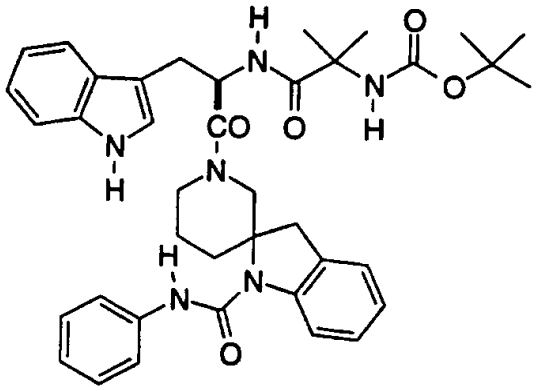
To a solution of the spiroamine (225 mg, 0.73 mmol) in CH_2Cl_2 was added EDCI (281 mg, 1.46 mmol), HOBt (99 mg, 0.73 mmol) and N-BOC-d-Trp (223 mg, 0.73). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K2CO3, water, brine, dried (Na_2SO_4), filtered and concentrated to give 420 mg of the title compound: MS (CI) 594.3 (M+H).

Step D:



The N-BOC derivative was deprotected as described above with TFA/CH_2Cl_2 to give the title compound: MS (CI) 494.3 (M+H).

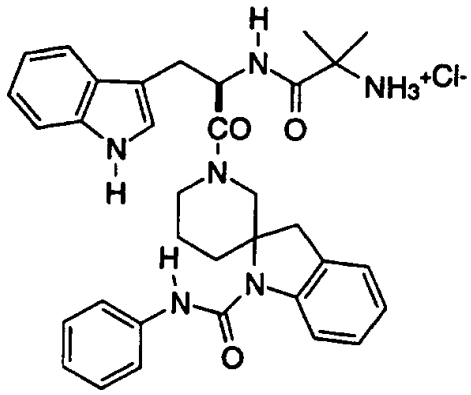
Step E:



To a solution of the amine (174 mg, 0.32 mmol) in CH_2Cl_2 was added EDCI (123 mg, 0.64 mmol), HOBt (44 mg, 0.32 mmol) and N-BOC amino iso-butyric acid (65 mg, 0.32 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filterd and concentrated. Radial chromatography (2 mm plate, 1:1 hexanes:ethyl acetate) gave 83 mg of the higher Rf diastereomer and 52 mg of the lower Rf diastereomer: MS (CI) higher Rf

diastereomer 679.3 (M+H); MS (CI) lower Rf diastereomer 679.3 (M+H).

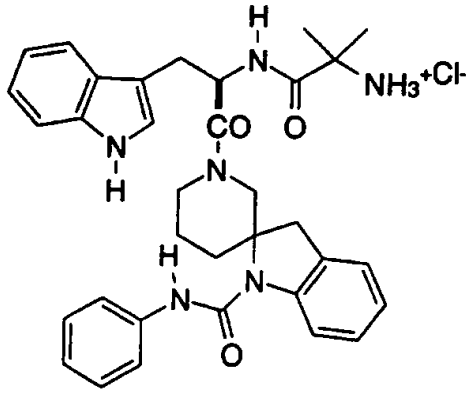
Step F:



Diastereomer #1 (higer Rf)

Deprotection of the N-BOC derivative gave the title compound: MS(CI) 579.2 (M+H).

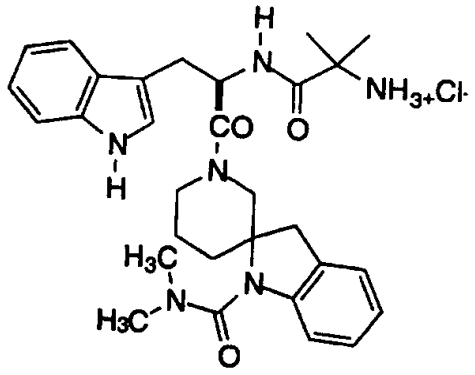
Step G:



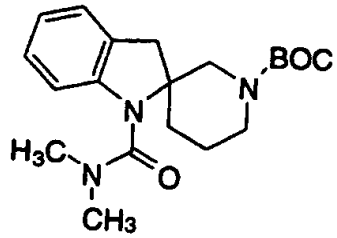
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative gave the title compound: MS (CI) 579.3 (M+H).

EXAMPLE A9

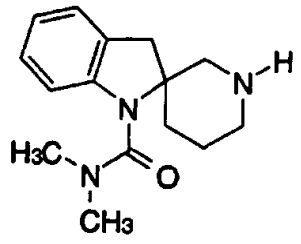


Step A:



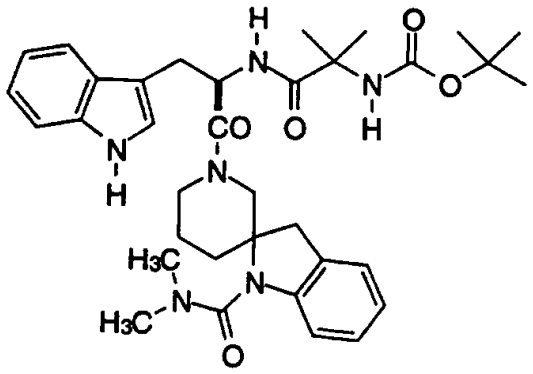
To a 0°C solution of the aniline (189 mg, 0.58 mmol) in THF (5 mL) was added KHMDS (1.28 mL of a 0.5 M solution , 0.65 mmol). The reaction was stirred for 5 minutes at 0°C wherupon N,N dimethylcarbamoyl chloride (0.11 mL, 0.12 mmol) was added. The reaction was stirred for approximately 20 minutes then diluted wih ethyl acetate, washed with 2N HCl, sat. K_2CO_3, brine, dried, filtered and concentrated. Radial chromatography (2 mm plate, 4:1 hexanes:ethyl acetate) gave 120 mg of the title compound: MS (CI) 360.3 (M+H), 327.3, 304.3.

Step B:



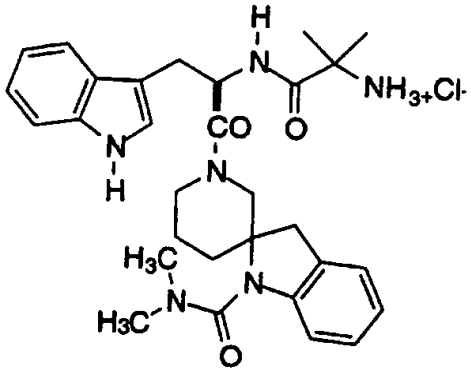
Deprotection of the N-BOC spirocycle (120 mg) with HCl/EtOAc gave 77 mg of the title amine after basic workup: MS (CI) 260.3 (M+H), 215.3 .

Step C:



To a solution of the spiroamine (76 mg, 0.29 mmol) in CH_2Cl_2 was added EDCI (112.6 mg, 0.58 mmol), HOBt (38.4 mg, 0.29 mmol) and d-Trp-N-BOC-AIB (114.5 mg, 0.29 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated. Radial chromatography (2 mm plate; 1:2 hexanes:ethyl acetate) of the residue gave 80 mg of the higher Rf diastereomer: MS(CI) 631.4 (M+H), 558.4, 557.4, 531.4 and 50 mg of a lower Rf diastereomer: MS(CI) 631.4 (M+H), 557.3, 531.4, 428.3.

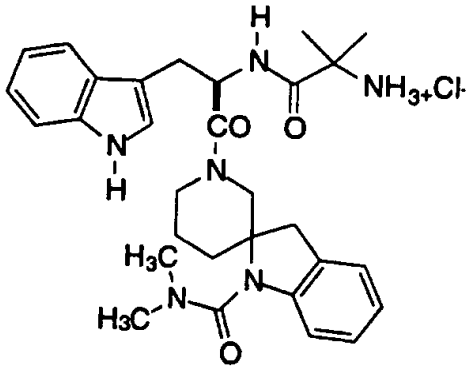
Step D:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 531.1 (M+H).

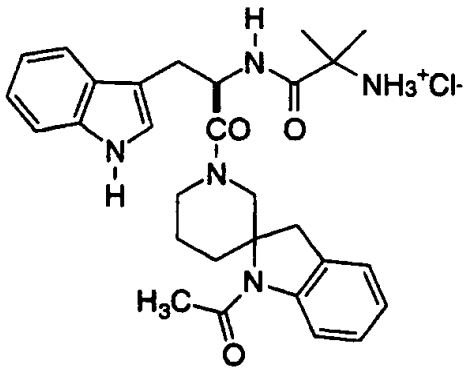
Step E:



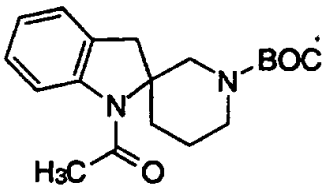
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 531.3 (M+H).

EXAMPLE A10

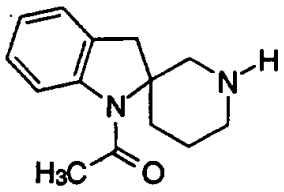


Step A:



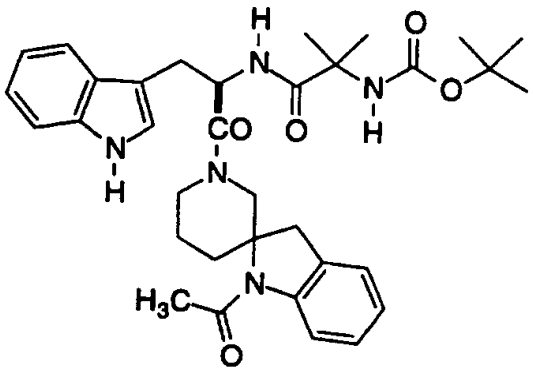
To a 0°C solution of the aniline (200 mg, 0.69 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (2.78 mL) and acetic anhydride (0.65 mL, 6.9 mmol). The reaction was stirred overnight at reflux. The following morning the reaction was diluted wih ethyl acetate, washed with 2N HCl, sat. K_2CO_3, brine, dried, filtered and concentrated. Chromatography (9:1 hexanes:ethyl acetate) gave 131 mg of the title compound: MS(CI) 231.2 (M+H-CO_2t-Bu), 170.1.

Step B:



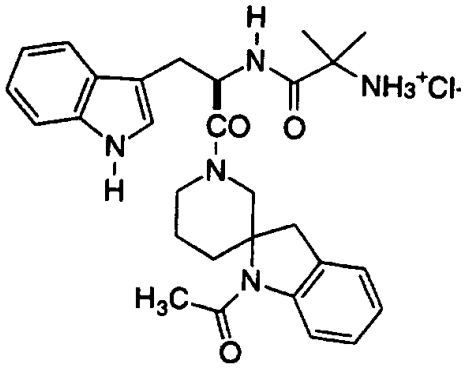
Deprotection of the N-BOC spirocycle (131 mg) with TFA/CH_2Cl_2 gave the title amine after basic workup: MS (CI) 231.2 (M+H), 181.1, 169.1.

Step C:



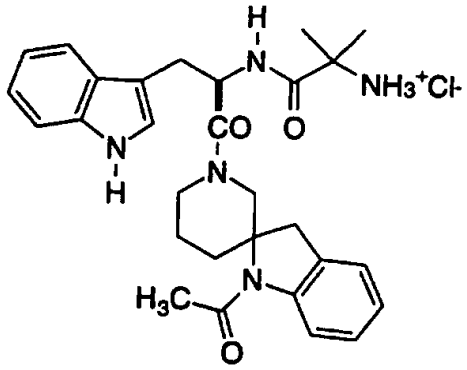
To a solution of the spiroamine (100 mg, 0.43 mmol) in CH_2Cl_2 was added EDCI (166.2 mg, 0.87 mmol), HOBt (58.6 mg, 0.43 mmol) and d-Trp-N-BOC-AIB (169.2 mg, 0.43 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated. Radial chromatography (2 mm plate; 2:1 hexanes:ethyl acetate) of the residue gave 105 mg of the higher Rf diastereomer: MS(CI) 602.4 (M+H), 528.3, 502.3 and 58 mg of a lower Rf diastereomer: MS(CI) 602.4 (M+H), 528.3, 502.3.

Step D:



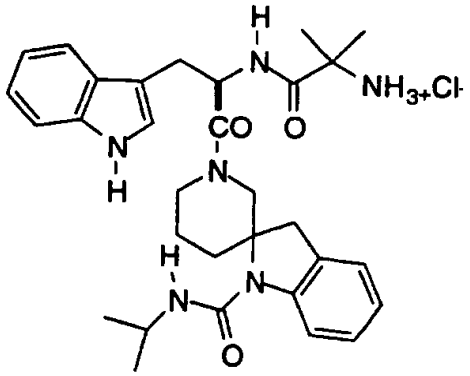
Diastereomer #1 (higher Rf)
Deprotection of the N-BOC derivative with TFA/CH_2Cl_2 gave the title compound: MS(CI) 502.2 (M+H), 444.2.

Step E:

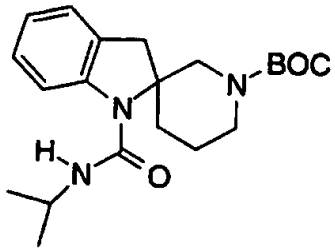


Diastereomer #2 (lower Rf)
Deprotection of the N-BOC derivative with TFA/CH_2Cl_2 gave the title compound: MS(CI) 502.2 (M+H).

EXAMPLE A11

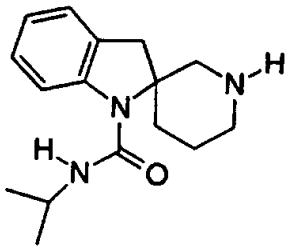


Step A:



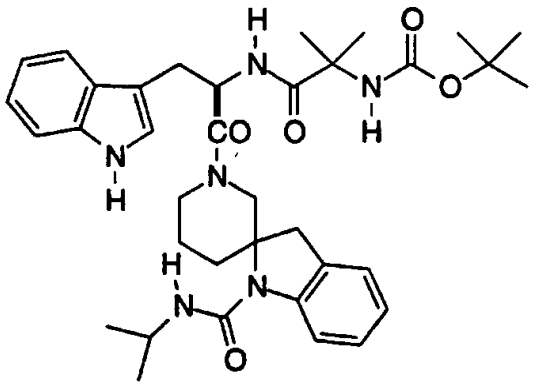
To a solution of the aniline (120 mg, 0.42 mmol) in toluene (3.0 mL) was added isopropyl isocyanate (0.41 mL, 4.2 mmol). The reaction was stirred at reflux until complete by TLC analysis whereupon it was diluted with ethyl acetate and washed with 2N HCl, sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Radial chromatography (6:1 hexanes:ethyl acetate) of the residue gave 90.4 mg the title compound.

Step B:



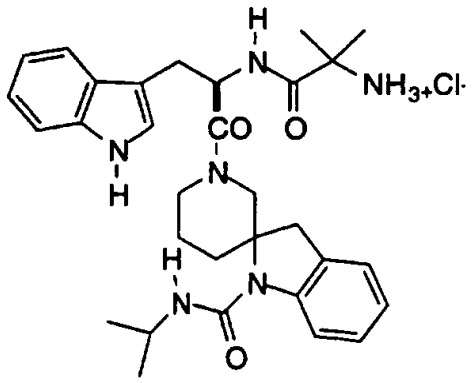
Deprotection of the N-BOC spirocycle (131 mg) with HCl/EtOAc gave the title amine after basic workup.

Step C:



To a solution of the spiroamine (63 mg, 0.23 mmol) in CH_2Cl_2 was added EDCI (88 mg, 0.46 mmol), HOBt (31 mg, 0.23 mmol) and d-Trp-N-BOC-AIB (Intermediate 1; 89.7 mg, 0.23 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated. Radial chromatography (2 mm plate; 1:2 hexanes:ethyl acetate) of the residue gave 36.5 mg of the higher Rf diastereomer: MS(CI) 654.4 (M+H), 486.3, 460 and 41 mg of a lower Rf diastereomer: MS(CI) 654.4 (M+H), 486.3, 460.3.

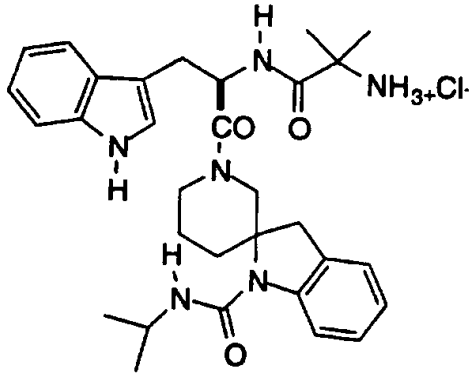
Step D:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 545.3 (M+H), 460.2, 274.1.

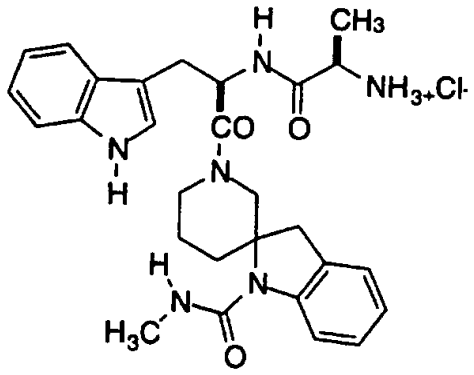
Step E:



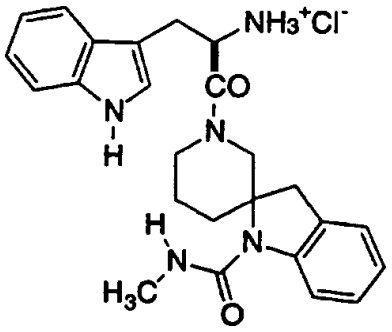
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 545.3 (M+H), 460.2, 274.1.

EXAMPLE A12

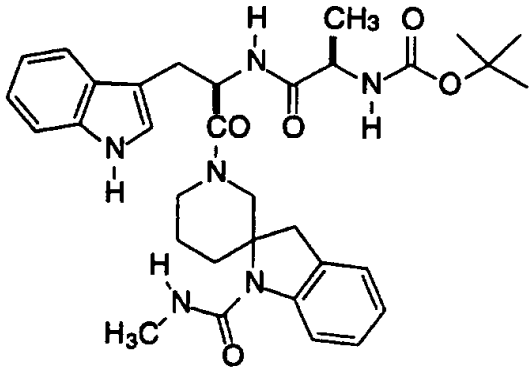


Step A:



To a solution of the spiroamine (650 mg, 2.64 mmol) in CH_2Cl_2 was added EDCI (1.01 g, 5.28 mmol), HOBt (356 mg, 2.64 mmol), N-methyl morpholine (0.29 mL, 2.64 mmol) and N-BOC-d-Trp (806 mg, 2.64 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated: MS(CI) 532.2 (M+H), 432.1. Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 432.3 (M+H), 375.3, 242.1.

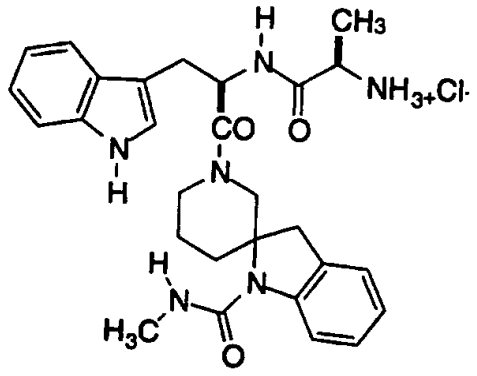
Step B:



The above amine salt was coupled to N-BOC-d-alanine in the usual manner. Radial chromatography (2 mm plate; 2:1 hexanes:ethyl acetate) of the residue gave 57.5 mg of the higher Rf

diastereomer: MS(CI) 603.1 (M+H) and 81.4 mg of a lower Rf diastereomer: MS(CI) 603.2 (M+H).

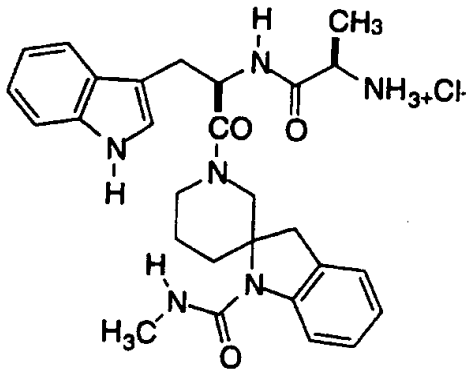
Step C:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 503.3 (M+H), 446.3.

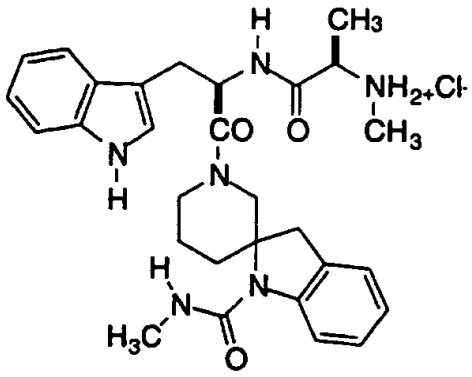
Step D:



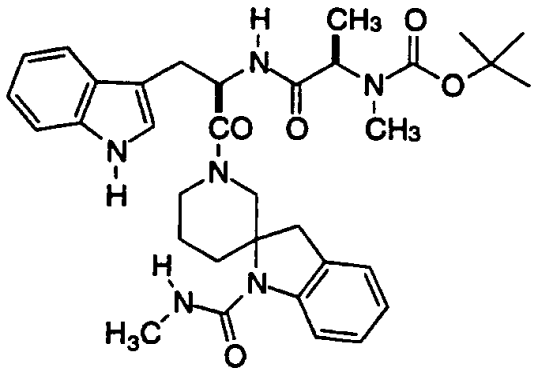
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 503.3 (M+H), 446.3.

EXAMPLE A13

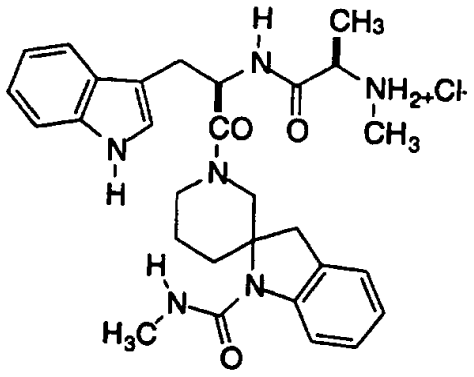


Step A:



The starting amine salt was coupled to N-methyl-N-BOC-d-alanine in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 34 mg of the higher Rf diastereomer: MS(CI) 617.2 (M+H) and 25 mg of a lower Rf diastereomer: MS(CI) 617.2(M+H).

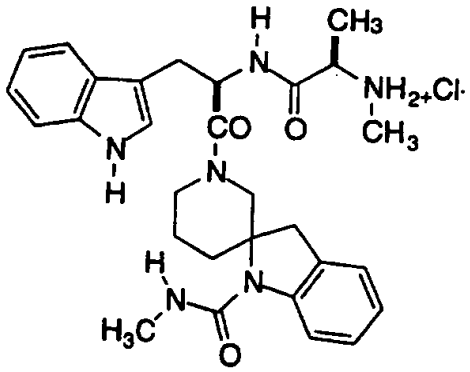
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 517.1 (M+H).

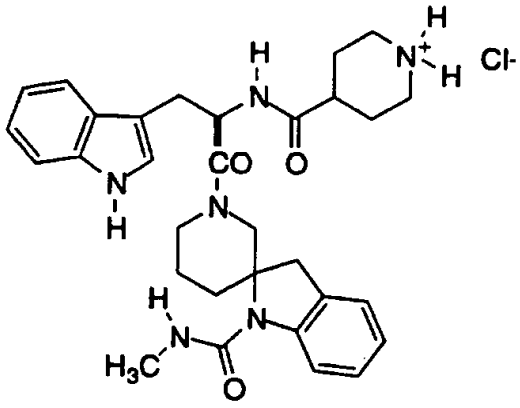
Step C:



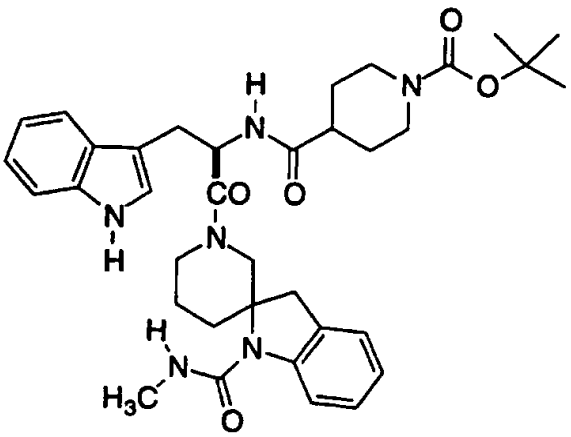
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 517.2 (M+H).

EXAMPLE A14

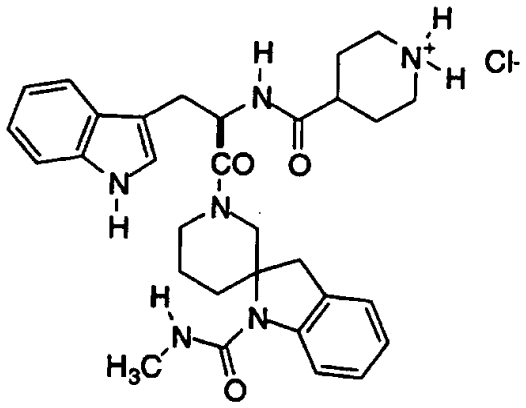


Step A:



The starting amine salt was coupled to N-BOC-iso-nipecotic acid in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 105.7 mg of the higher Rf diastereomer: MS (ESI) 643.2 (M+H) and 97.5 mg of a lower Rf diastereomer: MS (ESI) 643.2 (M+H).

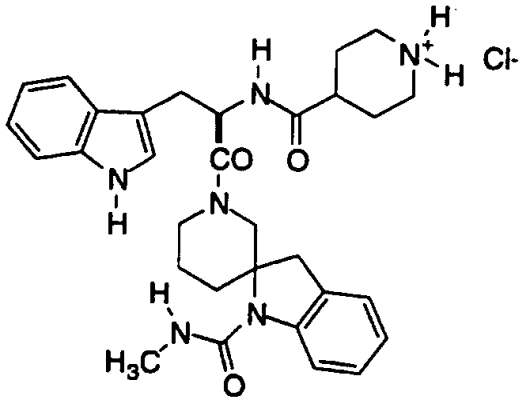
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 543.2 (M+H), 344.1.

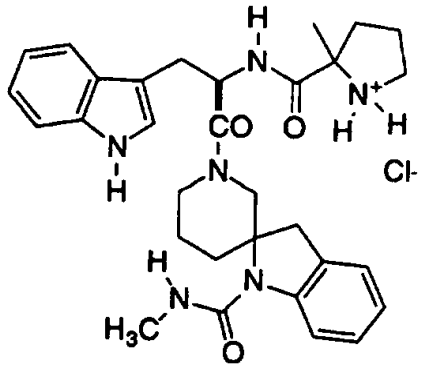
Step C:



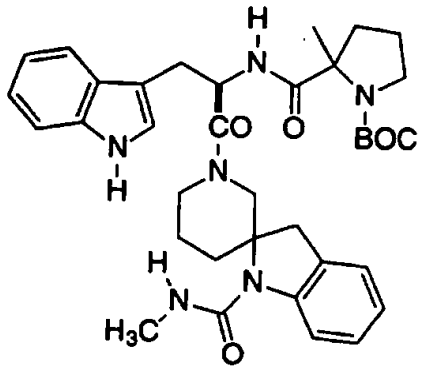
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(ESI) 543.2 (M+H), 344.0.

EXAMPLE A15

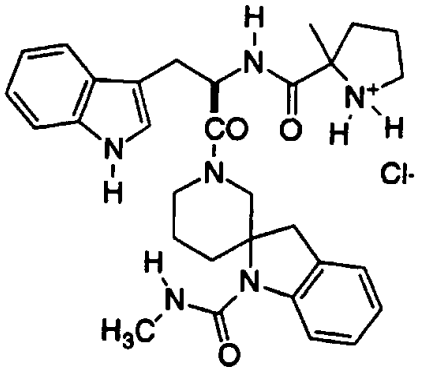


Step A:



The optically pure amine salt was coupled to N-BOC-a-methyl proline in the usual manner. Radial chromatography (2 mm plate; 6:4 hexanes:ethyl acetate) of the residue gave 45 mg of the higher Rf diastereomer: MS (ESI) 643.3 (M+H) and 36 mg of a lower Rf diastereomer: MS (ESI) 643.3 (M+H), 543.2, 246.0.

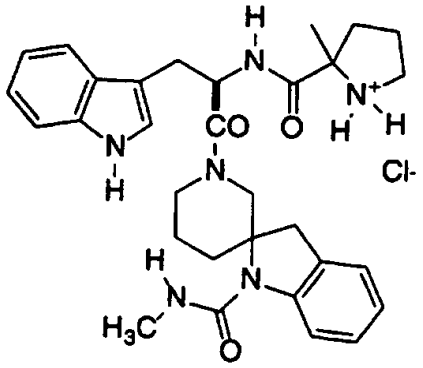
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 543.2 (M+H), 344.1.

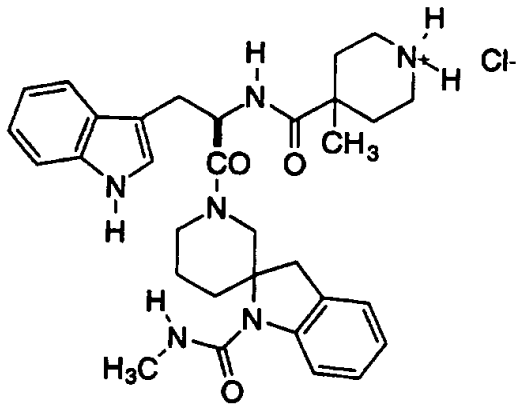
Step C:



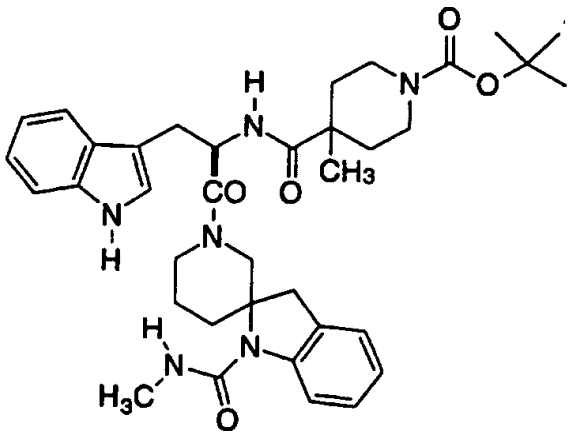
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(ESI) 543.2 (M+H), 486.1.

EXAMPLE A16

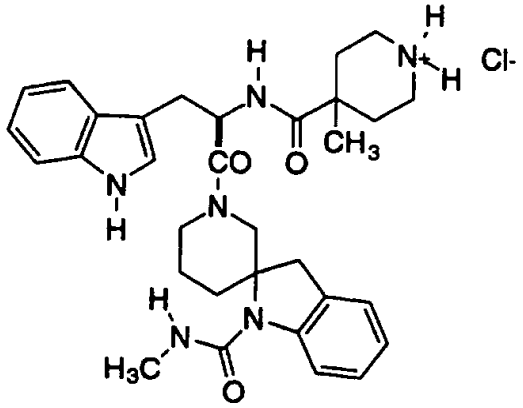


Step A:



The starting amine salt was coupled to α-methyl-N-BOC-iso-nipecotic acid in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 61.7 mg of the higher Rf diastereomer: MS(CI) 657.4 (M+H), 557.4, 500.3, 498.3, and 71.8 mg of a lower Rf diastereomer: MS(CI) 657.3 (M+H), 600.4, 500.3, 498.3.

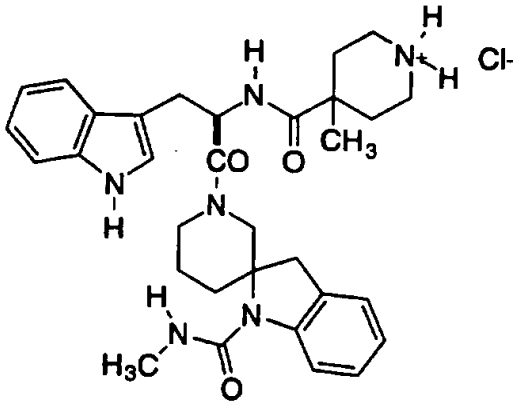
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 557.4 (M+H), 500.3, 358.3, 246.3.

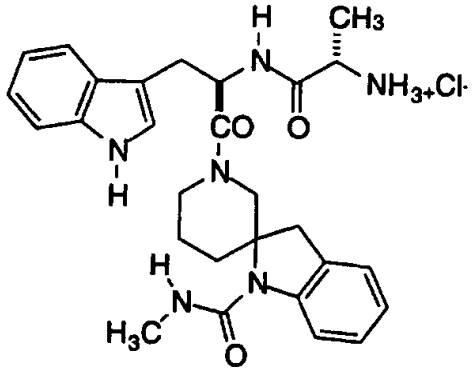
Step C:



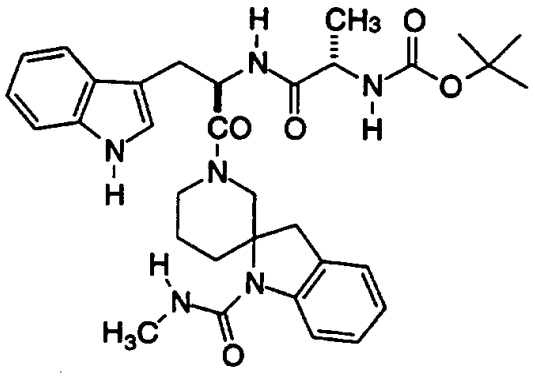
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 557.3 (M+H), 500.3, 498.3, 358.3, 246.3.

EXAMPLE A17

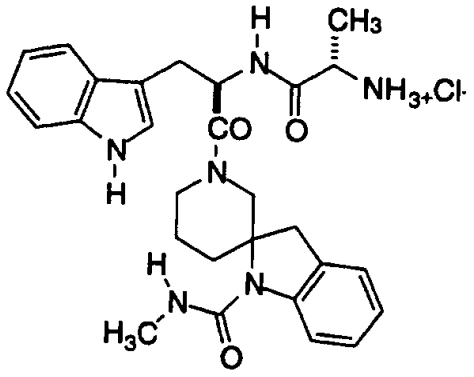


Step A:



The starting amine salt was coupled to N-BOC-l-alanine in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 48.1 mg of the higher Rf diastereomer: MS(ESI) 603.3 (M+H) and 50.9 mg of a lower Rf diastereomer: MS(ESI) 603.3 (M+H).

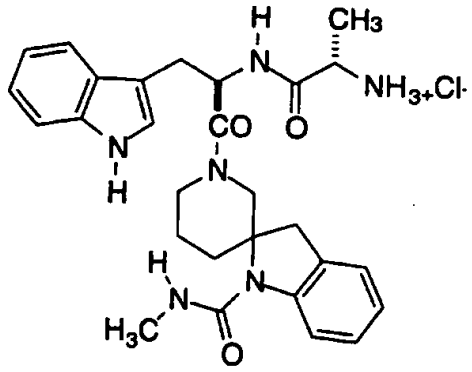
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 503.1 (M+H).

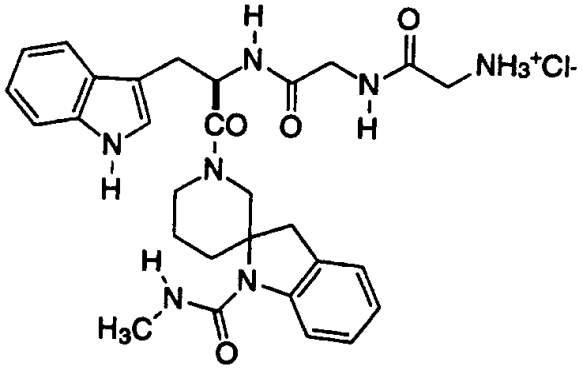
Step C:



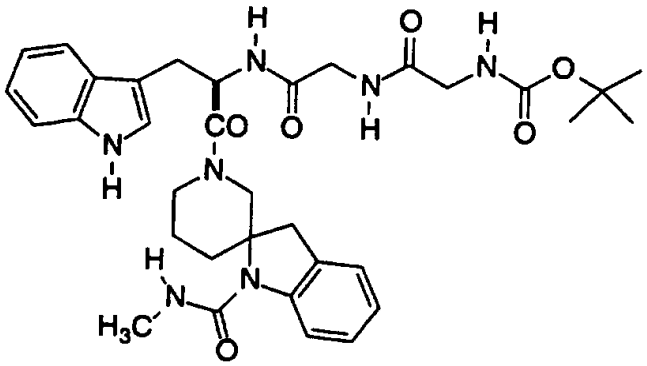
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 503.1 (M+H).

EXAMPLE A18

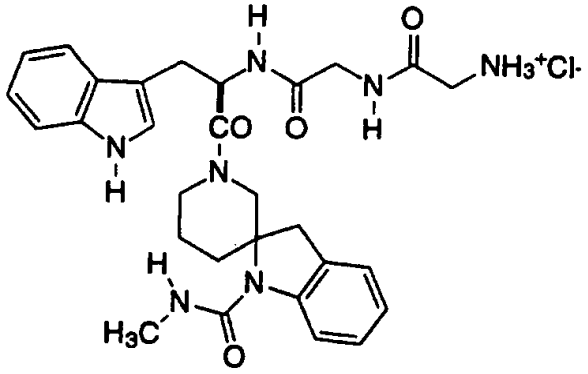


Step A:



The starting amine salt was coupled to N-BOC-sarcosine in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 48.1 mg of the higher Rf diastereomer: MS (ESI) 646.4 (M+H) and 50.9 mg of a lower Rf diastereomer: MS (ESI) 646.3 (M+H).

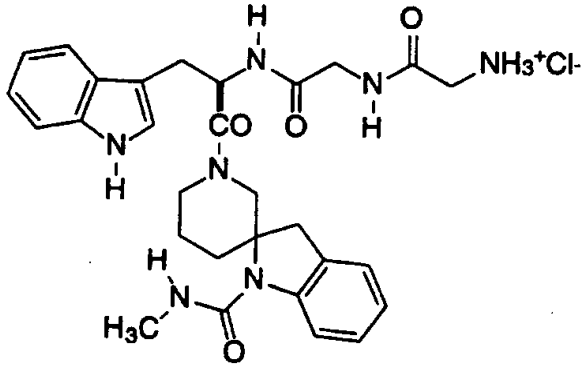
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 546.2 (M+H).

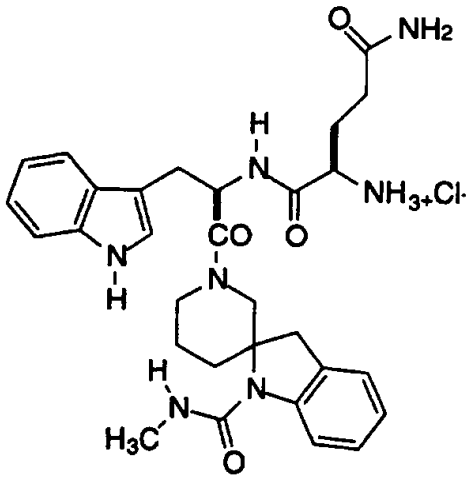
Step C:



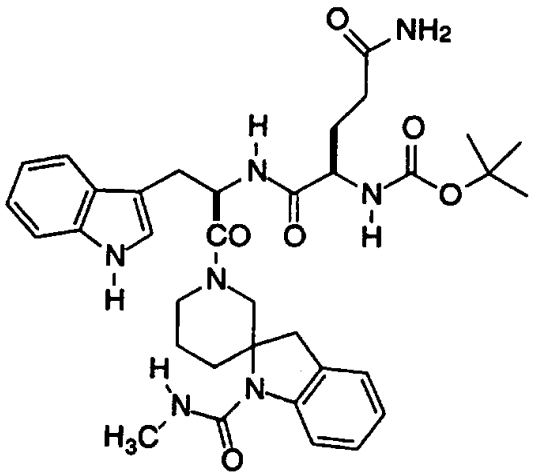
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 546.2 (M+H).

EXAMPLE A19

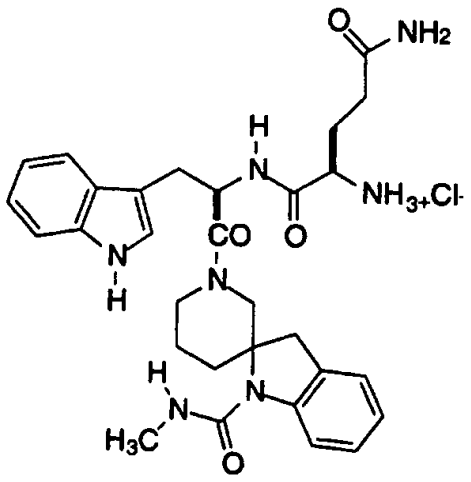


Step A:



The starting amine salt was coupled to N-BOC-d-Gln in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave 54.3 mg of the higher Rf diastereomer: MS (CI) 660.4 (M+H), 603.3, 529.4, 486.3, 263.2 and 65.3 mg of a lower Rf diastereomer: MS (CI) 660.4 (M+H), 603.4, 529.4, 486.3, 263.2, 246.3.

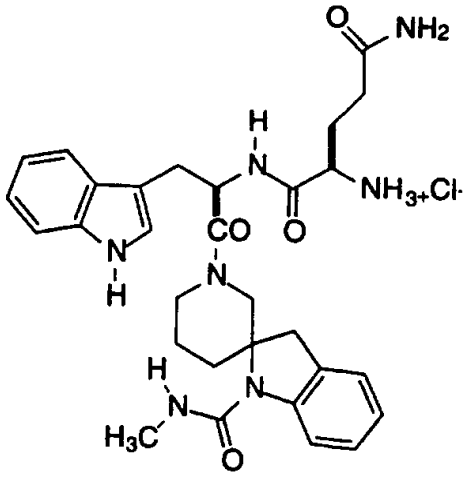
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 560.3 (M+H), 486.3.

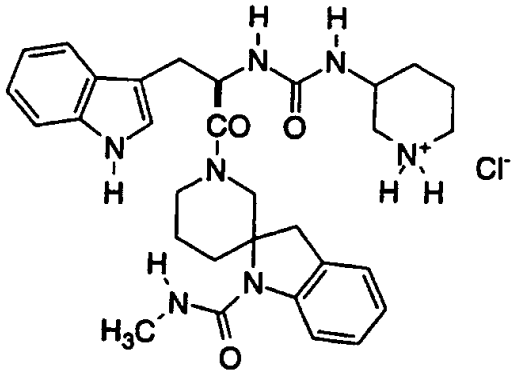
Step C:



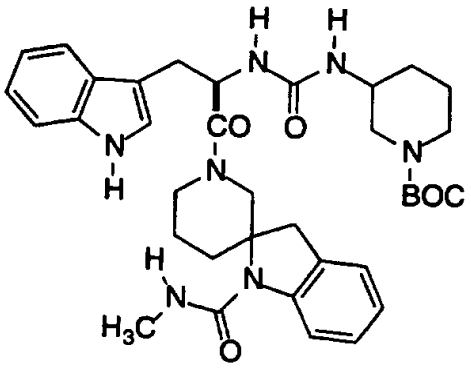
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 560.3 (M+H), 486.3.

EXAMPLE A20

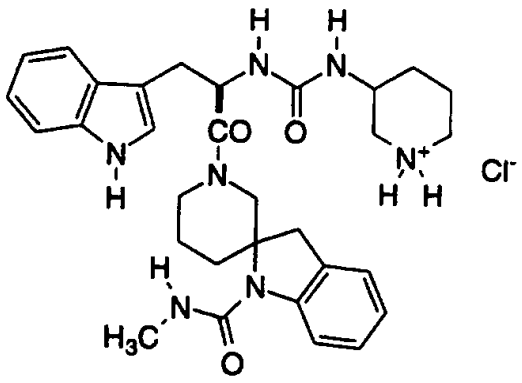


Step A:



To a solution of the starting amine salt (120 mg, 0.28 mmol) in CH_2Cl_2 (1.0 mL) was added N-methyl morpholine (35 uL, 0.31 mmol). The reaction was allowed to stir until the salt had completely dissolved whereupon a toluene solution of the isocyanate (0.21 mL of a 0.2 M solution in toluene, 0.42 mL) was added. The reaction was allowed to stir until complete as determined by TLC analysis. The reaction was then concentrated. Radial chromatography (2 mm plate, 4:1 EtOAc:hexanes) of the residue gave 53.3 mg of the higher Rf diastereomer: MS (ESI) 658.3 (M+H), 601.6, 500.1, 432.2 and 51.5 mg of a lower Rf diastereomer: MS (ESI) 658.3 (M+H), 601.1, 494.8, 472.1, 432.1.

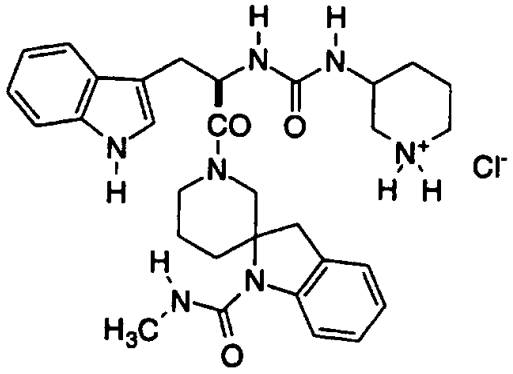
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 558.2 (M+H), 359.1.

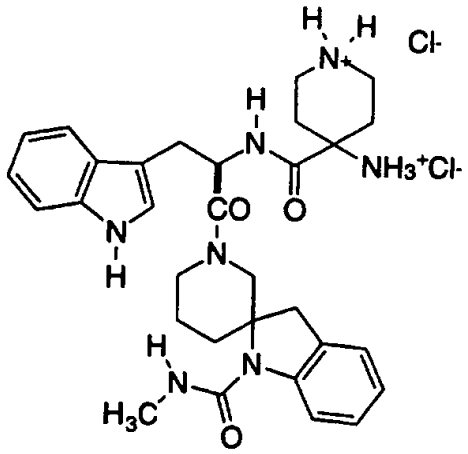
Step C:



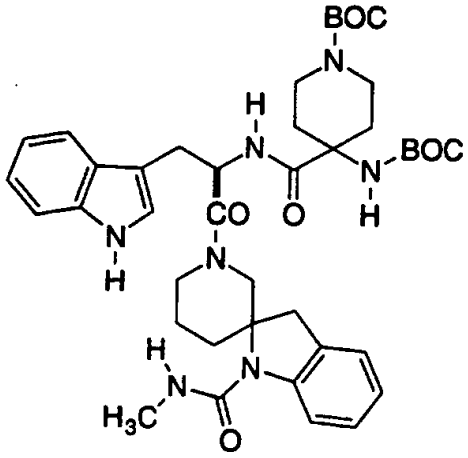
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 558.2 (M+H), 359.1, 246.0.

EXAMPLE A21

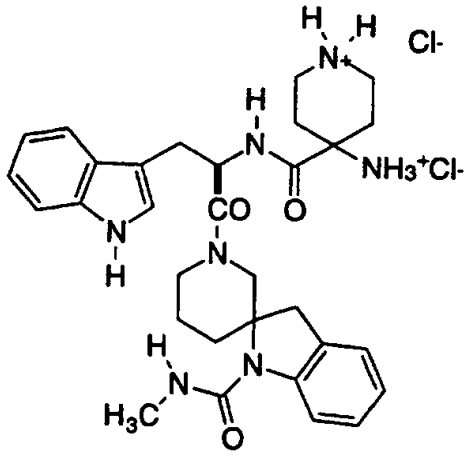


Step A:



The starting amine salt was coupled to the known di-N-BOC carboxylic acid in the usual manner. Radial chromatography (2 mm plate; 2:1 hexanes:ethyl acetate) of the residue gave 54.1 mg of the higher Rf diastereomer: MS (CI) 758.3 (M+H), 627.4, 601.4 and 102.8 mg of the lower Rf diastereomer: MS (CI) 758.4 (M+H), 701.3, 658.4, 627.4, 601.4.

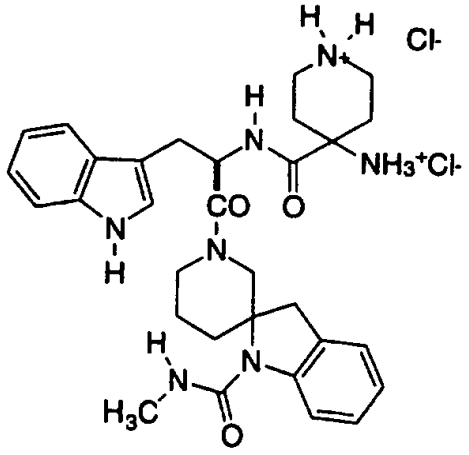
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the di-N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 558.4 (M+H), 501.3, 480.3.

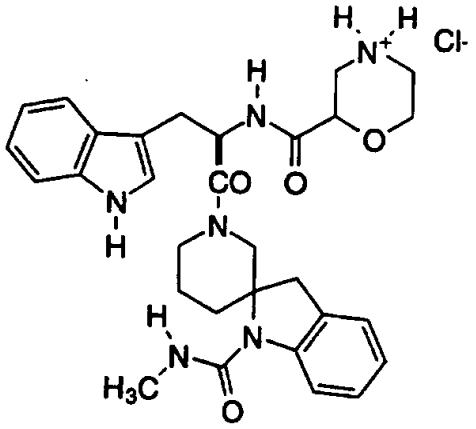
Step C:



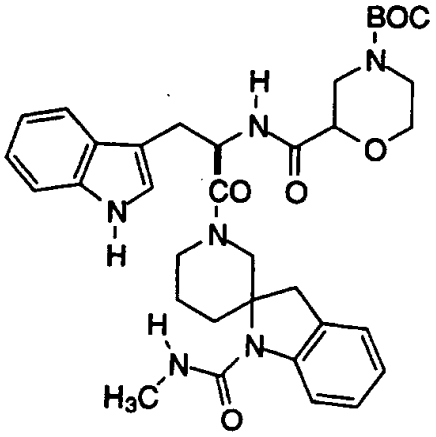
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 558.4 (M+H), 501.4, 480.3.

EXAMPLE A22

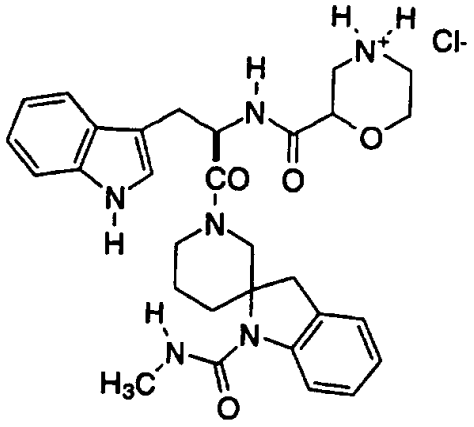


Step A:



The starting amine salt was coupled to 2-morpholine carboxylic acid in the usual manner. Radial chromatography (2 mm plate; 1:2 hexanes:ethyl acetate) of the residue gave 33.9 mg of the higher Rf diastereomer: MS(CI) 645.3 (M+H), 545.4, 488.3 and 27.0 mg of a lower Rf diastereomer: MS(CI) 645.3 (M+H), 588.3, 545.3.

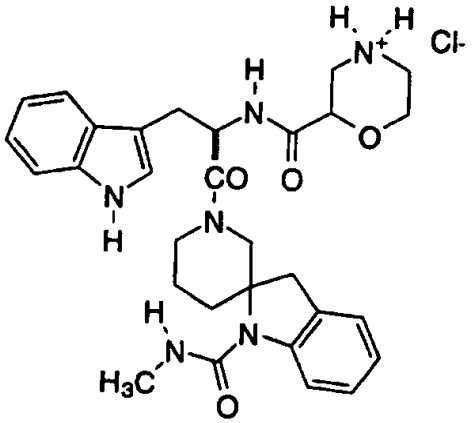
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 545.3 (M+H), 488.3.

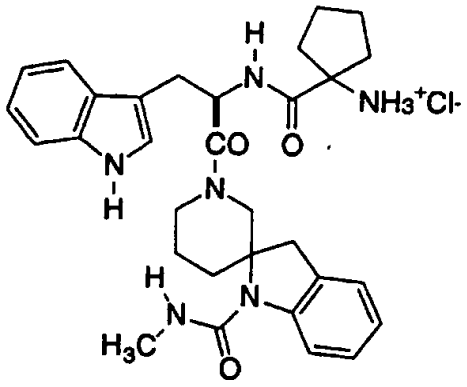
Step C:



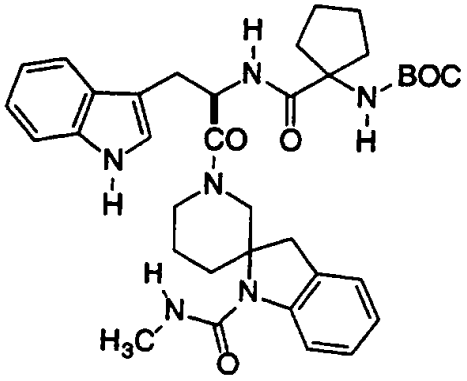
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(CI) 545.3 (M+H), 488.3.

EXAMPLE A23

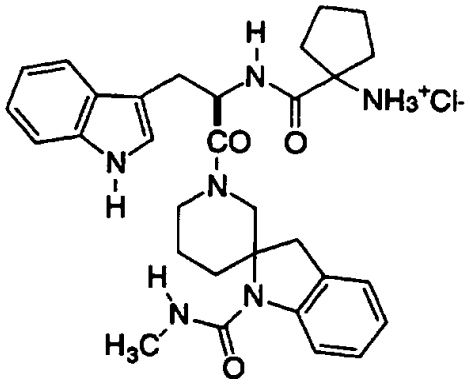


Step A:



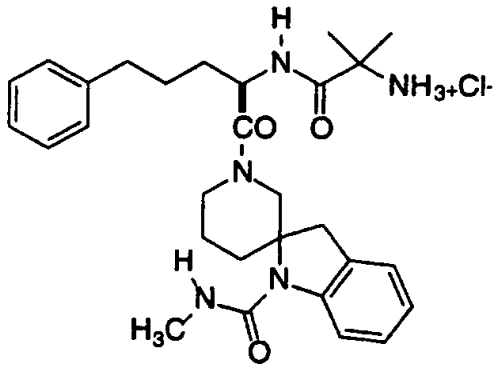
The starting optically pure amine salt was coupled to the carboxylic acid in the usual manner. Radial chromatography (2 mm plate; 1:4 hexanes:ethyl acetate) of the residue gave the title compound: MS(CI) 643.3 (M+H), 587.2, 543.2.

Step B:

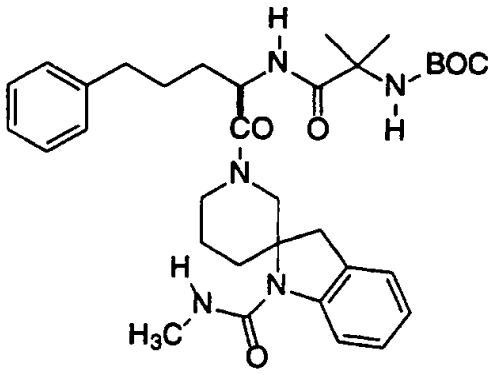


Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound.

EXAMPLE A24

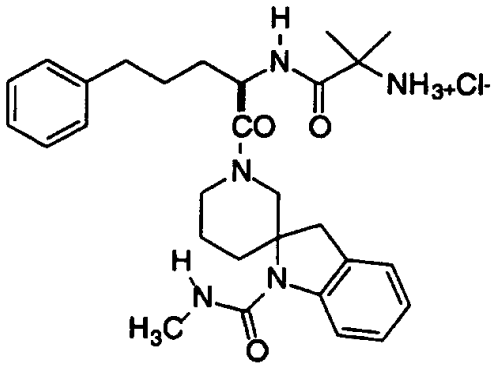


Step A:



To a solution of the N-methylurea spiroamine (75 mg, 0.31 mmol) in CH_2Cl_2 (3.0 mL) was added EDCI (117 mg, 0.61 mmol), HOBt (41.2 mg, 0.31 mmol), N-methyl morpholine (0.33 uL, 0.31 mmol) and the phenpropyl-N-BOC-AIB carboxylic acid (Intermediate 3; 117.8 mg, 0.31 mmol). The reaction was maintained at room temperature until complete by TLC whereupon it was diluted with ethyl acetate, washed with 2N HCl, sat. $NaHCO_3$, water, brine, dried (Na_2SO_4) and concentrated. Radial chromatography (2 mm plate; 4:1 ethyl acetate) gave 2 separate diastereomers: D1 (higher Rf): MS (CI) 606.3 (M+H), 532.3, 475.2, 449.3 : D2 (lower Rf): MS (CI) 606.4 (M+H), 532.3, 475.3, 449.3.

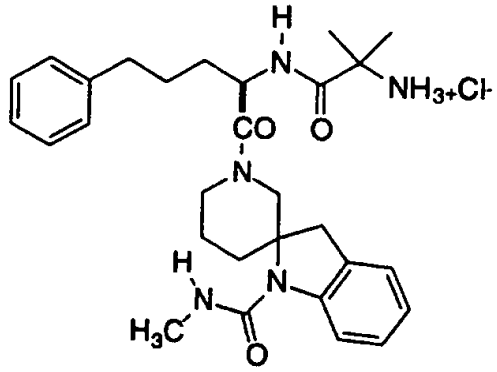
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 506.3 (M+H), 449.3, 307.2.

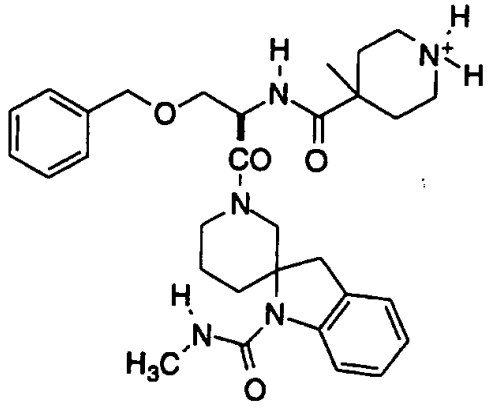
Step C:



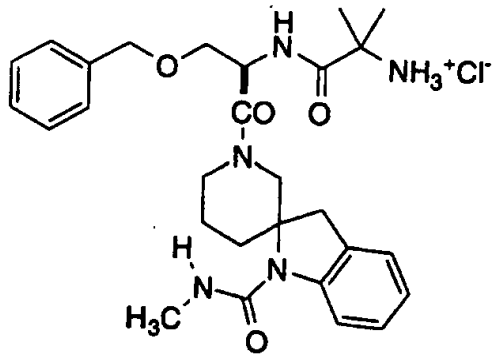
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (CI) 506.3 (M+H), 449.3, 307.2.

EXAMPLE A25

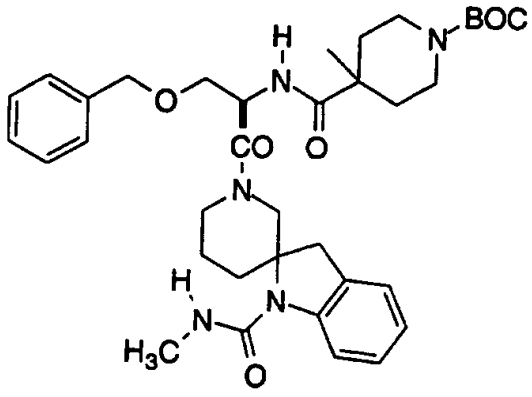


Step A:



To a solution of the N-methylurea spiroamine salt (100 mg, 0.41 mmol) in CH_2Cl_2 (5.0 mL) was added EDCI (156 mg, 0.81 mmol), HOBt (55 mg, 0.41 mmol), N-methyl morpholine (45 uL, 0.41 mmol) and benzyloxymethyl-N-BOC-AIB carboxylic acid (Intermediate 2; 122 mg, 0.41 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated to give 206 mg of the N-BOC derivative: MS (ESI) 523.2 (M+H), 423.2, 365.1. Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 423.2 (M+H).

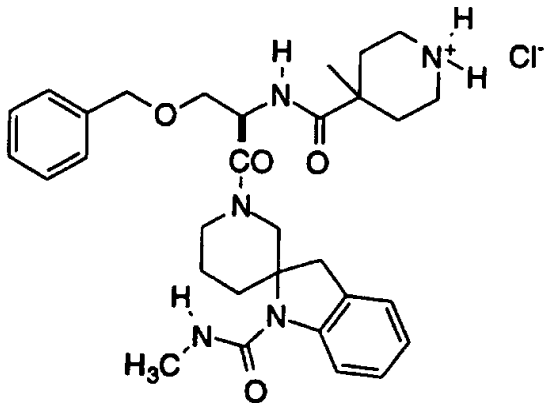
Step B:



The starting amine salt was coupled to a-methyl-N-BOC-iso-nipecotic acid in the usual manner. Radial chromatography (2 mm plate;

1:4 hexanes:ethyl acetate) of the residue gave 66.5 mg of the higher Rf diastereomer and 48.1 mg of a lower Rf diastereomer which were carried on to the deprotection step.

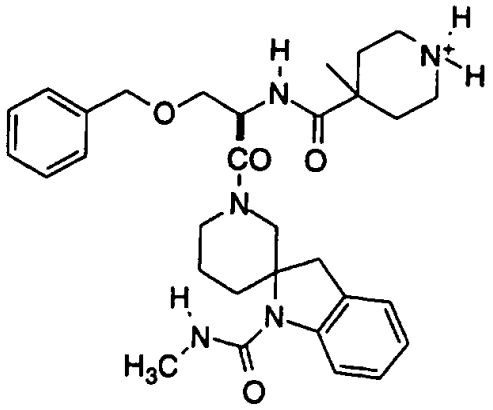
Step C:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 534.3 (M+H).

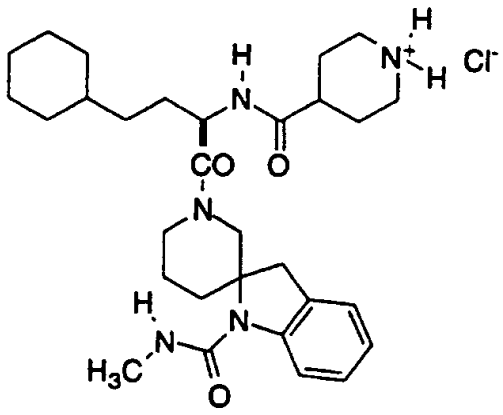
Step D:



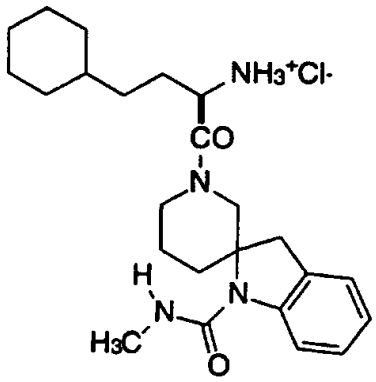
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 534.2 (M+H).

EXAMPLE A26

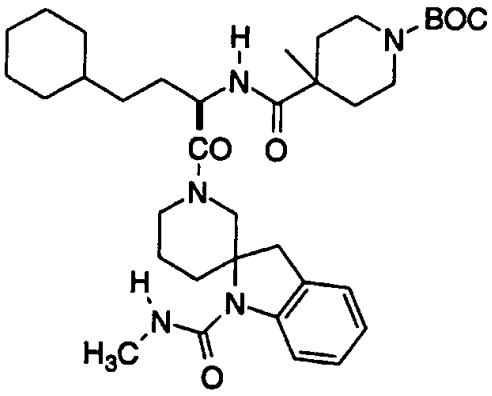


Step A:



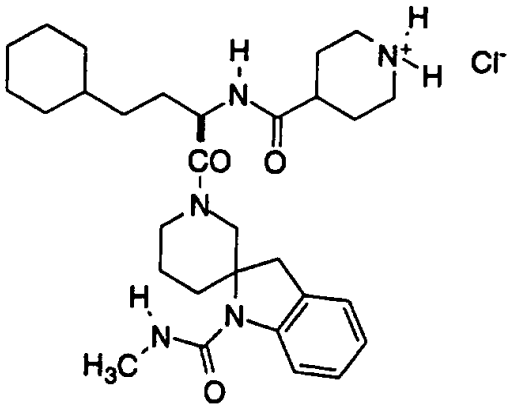
To a solution of the N-methylurea spiroamine salt (10o mg, 0.41 mmol) in CH_2Cl_2 (3.0 mL) was added EDCI (156 mg, 0.81 mmol), HOBt (55 mg, 0.41 mmol), N-methyl morpholine (45 uL, 0.41 mmol) and cyclohexylethyl-N-BOC-AIB carboxylic acid (122 mg, 0.41 mmol). The reaction was allowed to stir until complete by TLC analysis. The reaction was diluted with ethyl acetate and washed with 2N HCl, sat. K_2CO_3, water, brine, dried (Na_2SO_4), filtered and concentrated to give 174 mg of the N-BOC derivative: MS (ESI) 513.1 (M+H). Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 413.1 (M+H).

Step B:



The starting amine salt was coupled to a-methyl-N-BOC-isonipecotic acid in the usual manner. Radial chromatography (2 mm plate; 1:2 to 1:4 hexanes:ethyl acetate to 100% CH_3OH) of the residue gave 58.4 mg of the higher Rf diastereomer: MS (ESI) 624.2 (M+H) and 66.3 mg of a lower Rf diastereomer: MS (ESI) 624.2 (M+H).

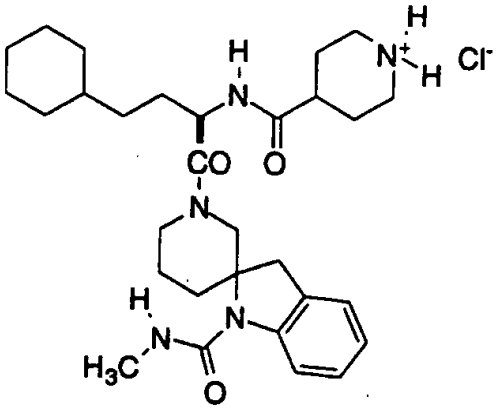
Step C:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS(ESI) 524.3 (M+H).

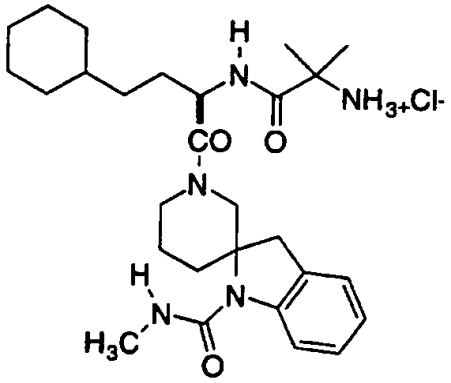
Step D:



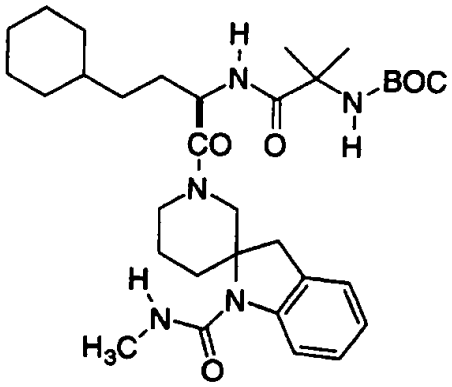
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 524.2 (M+H).

EXAMPLE A27

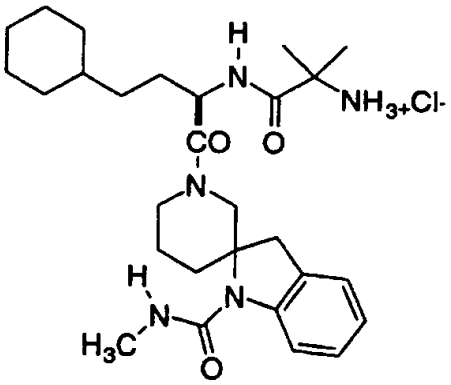


Step A:



The starting amine salt was coupled to N-BOC-AIB carboxylic acid in the usual manner. Radial chromatography of the residue gave 27 mg of the higher Rf diastereomer: MS (ESI) 598.4 (M+H), 498.3, and 22 mg of a lower Rf diastereomer: MS (ESI) 598.4 (M+H), 498.3.

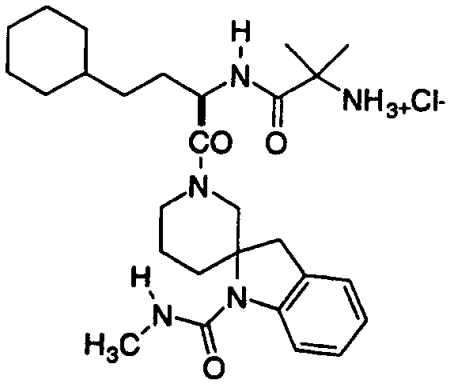
Step B:



Diastereomer #1 (higher Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 498.2 (M+H).

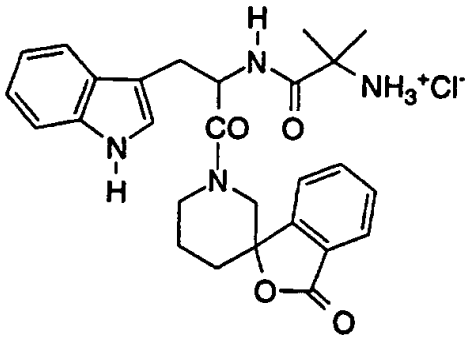
Step C:



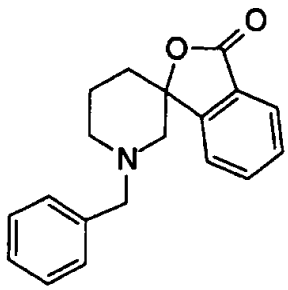
Diastereomer #2 (lower Rf)

Deprotection of the N-BOC derivative with HCl/EtOAc gave the title compound: MS (ESI) 498.2 (M+H).

EXAMPLE B1

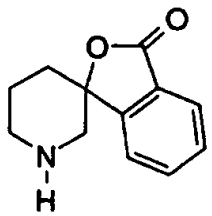


Step A:



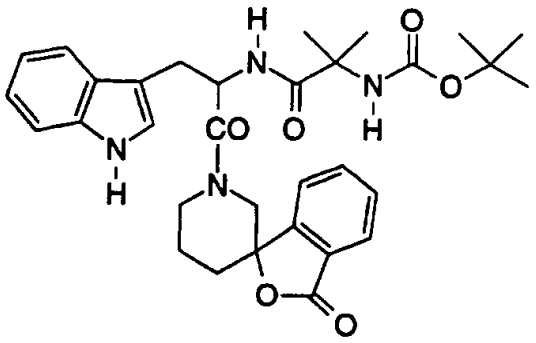
To a -78°C solution of o-bromo benzoic acid (2.0 g, 9.9 mmol) in THF (30 mL) was added n-BuLi (13.5 mL of a 2.5 M solution, 33.8 mmol). The reaction was maintained at -78°C for 2 hours whereupon a THF solution of N-benzyl piperidinone (2.9 g, 14.9 mmol) was added dropwise via syringe. The reaction was maintained at -78°C for 30 minutes whereupon it was diluted with ether and water. The water layer was extracted with ether (2 times). The water layer was made acidic with conc. HCl (pH=2-3) and heated to reflux for 10 hours after which the reaction was colled to room temperature and the pH was adjusted to pH=9-10 with 5N NaOH and extracted with ether (3x100mL). The combined organic layers were washed with brine, dried (MgSO4) and concentrated. Column chromatography of the residue (4:1 hexanes : ethyl acetate) gave 490 mg of the title compound: MS(CI) 294 (M+1).

Step B:



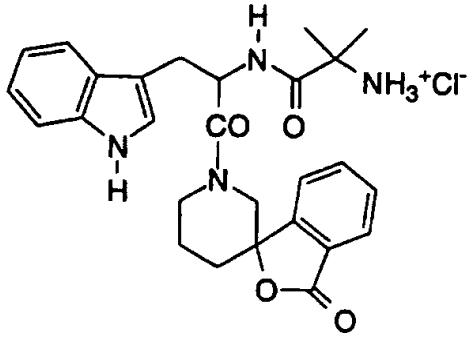
To a solution of the N-benzyl spirolactone (0.45 g; 1.53 mmol) in dichloroethane (10 mL) was added ACE-Cl (0.21 mL; 1.99 mmol). The reaction was heated to reflux for 1.5 hours whereupon the it was cooled to room temperature and concentrated. The residue was then dissolved in dry methanol (10 mL) and heated to reflux for 2 hours, cooled to room temperature, concentrated and diluted with ether. The ether soulution was washed with saturated K_2CO_3, brine, dried (K_2CO_3) and concentrated. Column chromatography (5:1 CH_2Cl_2:CH_3OH) of the residue gave 220 mg of the title compound. MS(ESI) 204 (M+1).

Step C:



To solution of the amine (100 mg, 0.49 mmol) in CH_2Cl_2 (5.0 mL) was added HOBt (66.5 mg, 0.49 mmol), N-methyl morpholine (34.1 µL, 0.49 mmol), EDCI (188.6 mg, 0.98 mmol), and d-Trp-N-BOC-AIB (191.6 mmol, 0.49 mmol) (Intermediate 1). The reaction was allowed to stir overnight at room temperature whereupon it was diluted with ethyl acetate and washed with 2N HCL, saturated K_2CO_3, water, brine, dried (Na_2SO_4) and concentrated. Column chromatogroaphy (1:1 hexanes : ethyl acetate) of the residue gave the title compound. MS Found: d1 & d2 575 (M+1), 475, 272.

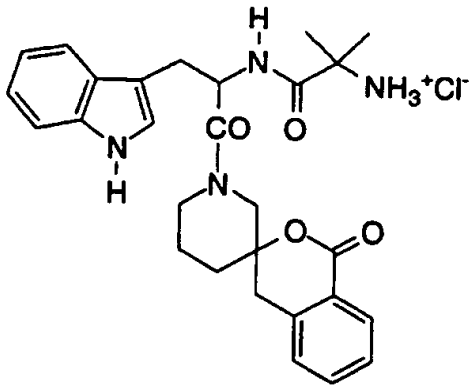
Step D:



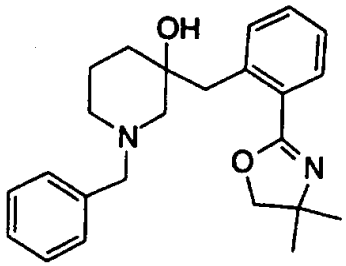
The diastereomers were dissolved in ethyl acetate saturated with HCl and stirred at room temperature until TLC analysis indicated that the starting material had been consumed. The reaction

was then concentrated in vacuo to give the title compound. MS Found: d1 & d2 475 (M+1), 318, 272.

EXAMPLE B2

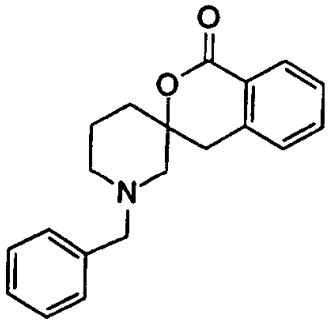


Step A:



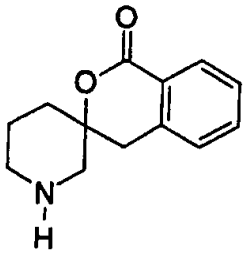
To a 0°C solution of the oxazoline (0.91 g, 4.8 mmol) in ether (18 mL) was added n-BuLi (5.81 mmol) dropwise. The deep red solution was stirred at 0°C for 1 hour whereupon a solution of N-benzyl-3-piperidinone (1.0 g, 5.28 mmol) was added dropwise. The reaction was allowed to warm to room temperature and quenched with 2N HCl. The aqueous layer was made basic with 5N NaOH and extracted with ether (3X). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography (1:1 hexanes : ethyl acetate) of the residue gave 460 mg (23%) of the title compound: MS(CI) 379 (M+1).

Step B:



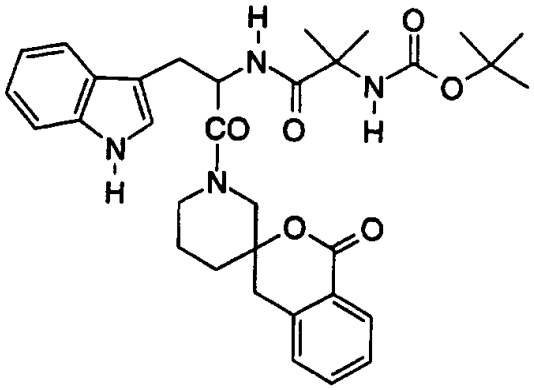
The oxazoline (250 mg) was dissolved in 1N HCl (50 mL) and heated to reflux until the starting material was completely consumed as determined by TLC analysis. To this reaction was added ether and the aqueous layer was made basic with 5N NaOH. The aqueous layer was extracted with ether (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue (1:1 hexanes : ethyl acetate) gave the title compound: MS(CI) 308 (M+1).

Step C:



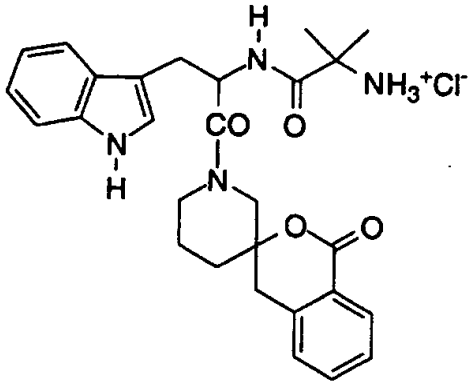
The compound was deprotected in the same manner as described in Example B1, Step B to give the title compound: MS(CI) 218 (M+1).

Step D:



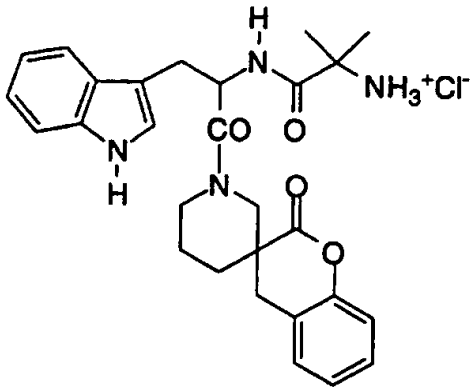
The 3-spiro lactone was coupled in the same manner as described in Example B1, Step C to give the title compound. MS Found: d1 & d2 589 (M+1), 545, 489.

Step E:

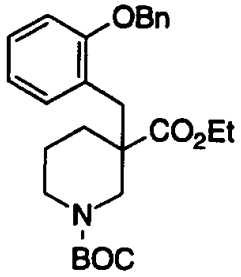


The compound from the previous step was deprotected in the same manner as described in Example B1, Step D to give the title compound. MS Found: d1 & d2 489 (M+1), 272, 218.

EXAMPLE B3

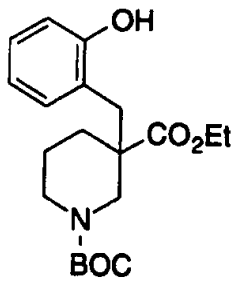


Step A:



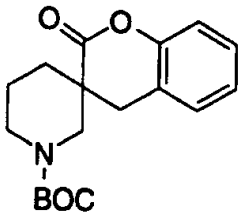
To a stirred solution of KHMDS (9.28 g) in THF (100 mL) at -78°C under argon, was added ethyl N-BOC nipecotate (9.6 g, 37.2 mmol) in THF (20 mL) over a 10 minute period. The solution was allowed to stir an additional 30 minutes at -78°C; then 2-benzyloxybenzyl choride (1 equiv.) was added slowly to the solution. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate (2 x 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography, eluting with a gradient of 0-30% ethyl acetate in hexane, provided the intermediate (8.44 g).

Step B:



A suspension of 10% palladium on carbon (200 mg) and the intermediate from the previous step (2.91 g) in ethanol (20 mL) was vigorously stirred under a hydrogen atmosphere for 30 minutes. The reaction mixture was then filtered through celite and evaporated to give the product (1.46 g): ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.09-7.00 (m, 2 H), 6.81-6.78 (m, 2H), 4.07-4.02 (m, 2H), 3.93 (br. d, J=13 Hz, 1H), 3.52-3.49 (m, 1H), 3.26 (d, J=13 Hz, 1H), 3.27-3.20 (br. m, 1H), 2.93 (d, J=14 Hz, 1H), 2.79 (d, J=14 Hz, 1H), 2.07-2.03 (m, 1H), 1.70-1.55 (m, 3H), 1.44 (s, 9H), 1.12 (t, J=7 Hz, 3H).

Step C:

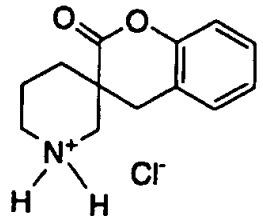


To a solution of the ethyl ester (250 mg) in ethanol (5 mL) was added 5 N NaOH (1 mL) and the reation was heated at 60°C overnight. The following morning the reaction was cooled to room temperature, made acidic with 3N HCl and extracted with ethyl acetate. The organic layer was dried and concentrated to give 0.27 g of the carboxylic acid which was carried on to the next step without purification.

To a solution of the carboxylic acid (0.27 g) in CH_2Cl_2 was added EDCI (300 mg) and DMAP (2 mg). The reaction was stirred at

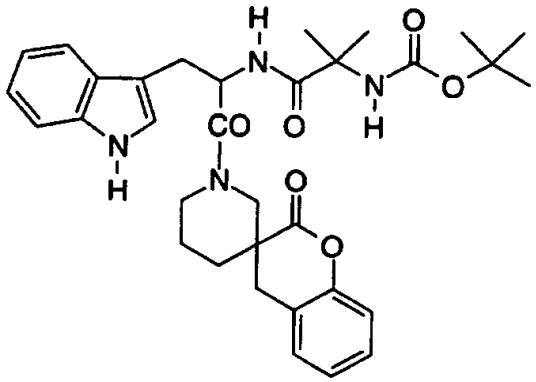
room temperature for 2 hours whereupon it was diluted with ethyl acetate and washed with brine, dried and concentrated. Column chromatography (20% ethyl acetate:hexanes) of the residue gave 160 mg of the 3-spiro lactone.

Step D:



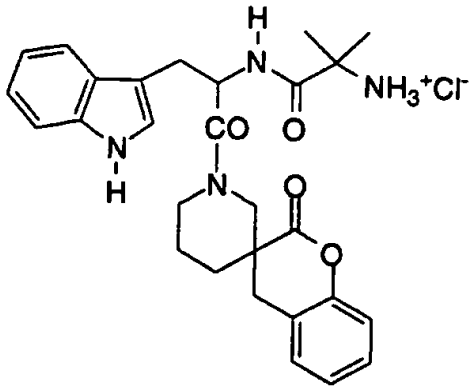
To stirred solution of the compound from the previous step (160 mg) in CH_2Cl_2/ether (1:5) was bubbled HCl gas. The reaction was stirred for 30 minutes then evaporated to dryness to give 127 mg of the amine salt: MS (CI) 218 (M+1).

Step E:



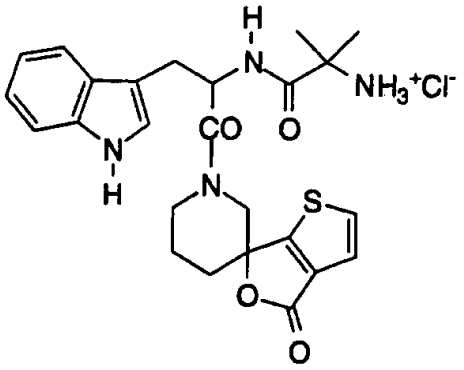
The amine salt was coupled to D-trp-N-BOC AIB in the same manner as described in Example B1, Step C to give the title compound. MS Found: d1 589 (M+1); d2 589 (M+1).

Step F:

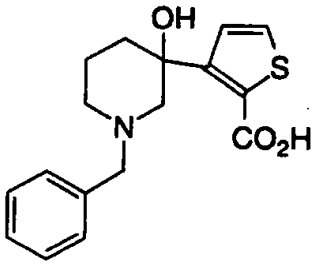


The compound from the previous step was deprotected in the same manner as described in Example B1, Step D. MS Found: d1 489 (M+1), 318, 218; d2 489 (M+1), 318, 218.

EXAMPLE B4

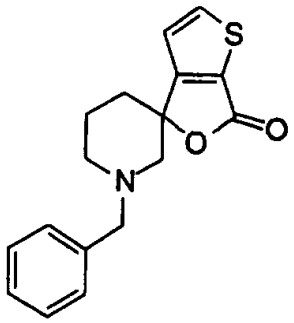


Step A:



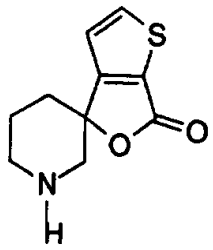
To a -74°C solution of 3-bromo thiophene (1.44 g, 8.84 mmol) in THF (13 mL) was added n-BuLi (5.52 mL of a 1.6 M solution in hexanes, 8.84 mmol). The reaction was stirred for 10 minutes whereupon N-benzyl 3-piperidinone (1.0 g, 8.84 mmol) in THF (6.5 mL) was added dropwise. The reaction was stirred at -78°C for 1 hour whereupon n-BuLi (5.52 mL of a 1.6 M solution in hexanes, 8.84 mmol) was added and the reaction was stirred for 1.5 hours and carbon dioxide gas was bubbled through the reaction mixture for 1.5 hours. The reaction was then stirred overnight at room temperature. The following morning the reaction was poured into ether and extracted with water (2x). The combined aqueous layers were acidified and washed with ether. The organic layer was concentrated to give 0.56 g of an orange solid: MS (ESI) 318 (M+1).

Step B:



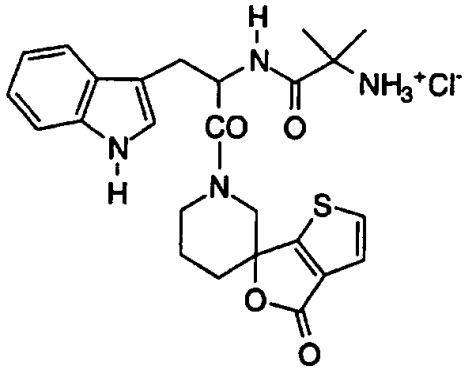
To a solution of the carboxylic acid (0.5 g, 1.58 mmol) from the previous step in $CHCl_3$:benzene (10 mL of a 2:1 mixture) was added sodium acetate (90 mg, 1.10 mmol) and acetic anhydride (0.54 mL, 5.67 mL) and refluxed for 4 hours whereupon saturated sodium carbonate (10 mL) was added and the reaction mixture was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were concentrated and the residue was chromatogrphed (19:1 CH_2Cl_2:EtOAc) to give the lactone: MS (ESI) 300 (M+1).

Step C:



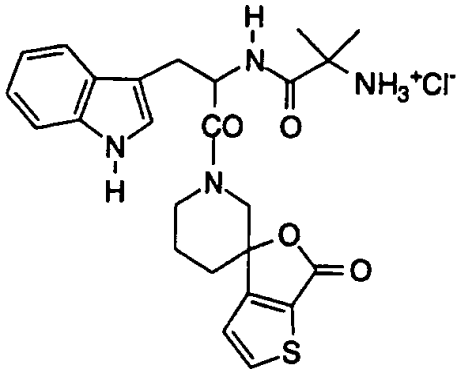
The N-benzyl 3-spiro lactone from the previous step was deprotected as described in Example B1, Step B to give the free amine: MS (ESI) 210 (M+1).

Step D:

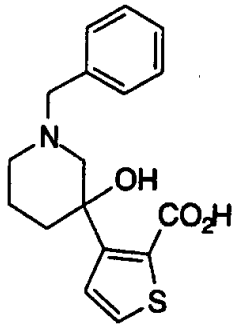


The amine from the previous step was coupled to D-trp-N-BOC AIB and deprotected as described in Example B1, Steps C and D to give the title compound. MS Found: d1 & d2 517, 370, 218.

EXAMPLE B5

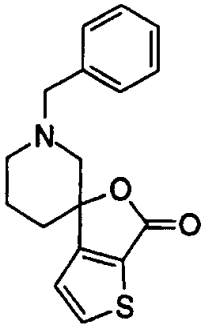


Step A:



To a -78°C solution of thiophene-2-carboxylic acid (0.56 g, 4.4 mmol) in THF was added LDA (13 mL of a 0.5 M solution) the reaction was maintained at -78°C for 1 hour whereupon a solution of the N-benzyl-3-piperidinone (1.0 g, 5.28 mmol) was added dropwise. The reaction was stirred at -78°C for 1 hour then poured into ether. The ether layer was washed with water (2x). The combined aqueous layers were made acidic and extracted with ether (2x). The combined organic layers were dried and concentrated to give the title compound: MS (ESI) 300 (M+1-H_2O).

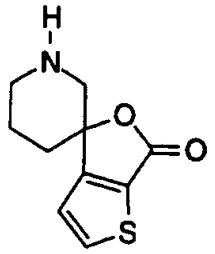
Step B:



To a solution of the hydroxy acid from the previous step (126 mg, 0.39 mmol) in dichloromethane (4 mL) was added EDCI (150 mmol, 0.78 mmol) and HOBT (53 mg, 0.39 mmol) the reaction was stirred overnight. The following morning the reaction was diluted with ethyl acetate and washed with water, brine, dried, concentrated and the

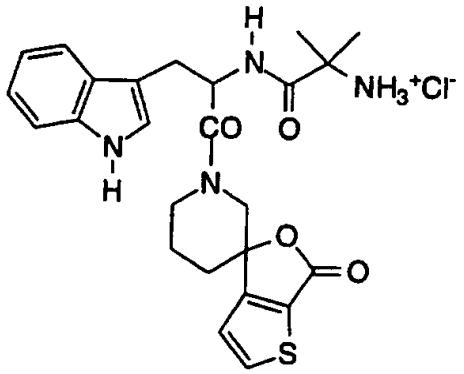
residue was chromatographed (2:1 hexanes:ethyl acetate) to give the title compound.

Step C:



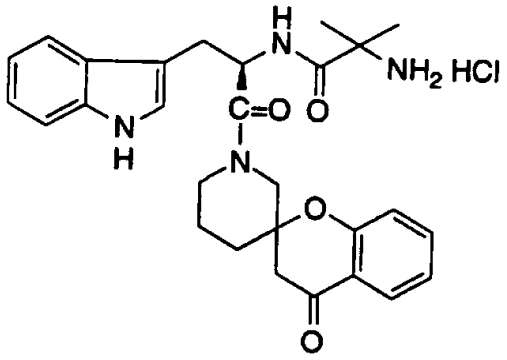
The N-benzyl-3-spirolactone from the previous step was deprotected as described in Example B1, Step B to give the corresponding amine.

Step D:

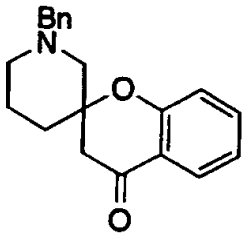


The amine from Step C was coupled to d-trp N-BOC AIB and subsequently deprotected as described in Example B1, Steps C and D to give the title compound. MS Found: d1 & d2 517, 393, 234, 218.

EXAMPLE C1

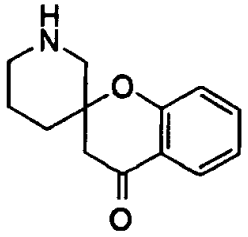


Step A:



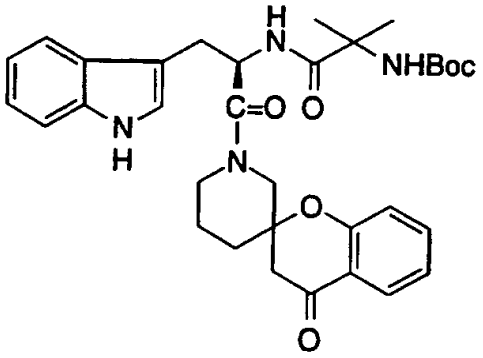
A mixture of N-benzyl-3-piperidine (5 g, 22 mmol), 2'-hydroxy acetophenone (3.02g, 22 mmol) and pyrrolidine (3.16 g, 44 mmol) in methanol (200 mL) was refluxed for 4 hours. The reaction mixture was evaporated to dryness and partitioned between ethyl acetate and sodium bicarbonate. The organic layer was extracted with 1 N HCl. The aqueous solution was neutralized and made slightly basic to pH 9 with 3 N NaOH, and the resulting solution was extracted with ethyl acetate. The organic layer was dried over MgSO4, filtered, evaporated and purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to yield the desired compound (3.56 g, 52%).

Step B:



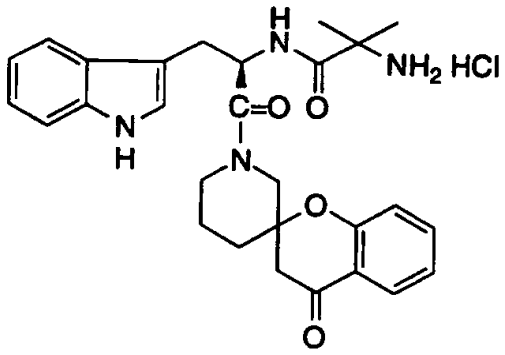
To a stirred solution of the intermediate obtained from previous step (3.5 g, 11.4 mmol) in dichloroethane was added alpha-chloroethyl chloroformate (ACE-Cl, 1.79 g, 12.5 mmol). The resulting solution was refluxed for 30 minutes and evaporated to dryness. The residue was dissolved in methanol (50 mL) and refluxed for 30 minutes. The solution was concentrated to 1/4 of the initial volume and the resulting crystals were collected (0.545 g). The mother liquor was poured into 0.3 N HCl and washed with ethyl acetate. The aqueous solution was made basic to pH 10 with 2 N NaOH, the suspension was extracted with ethyl acetate and then with chloroform. Purification by silica gel chromatography eluting with 2/20/80 NH_4OH/MeOH/ chloroform give the compound (1.825 g). The free base (1 g) was converted to the corresponding HCl salt by bubble HCl gas into the solution in ethyl acetate followed by evaporation.

Step C:



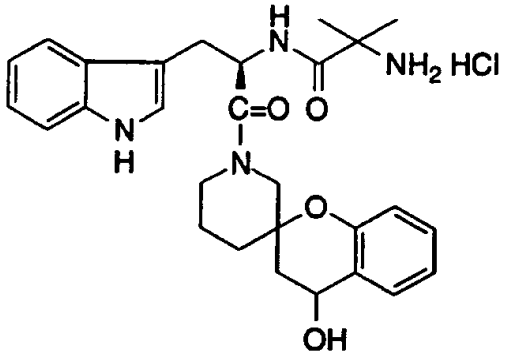
To a solution of the intermediate prepared in the previous step (110 mg, 0.43 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane at 0°C, was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (225 mg, 88%). FAB-MS calc. for C33H40N4O6: 588; Found 589 (M+H)

Step D:



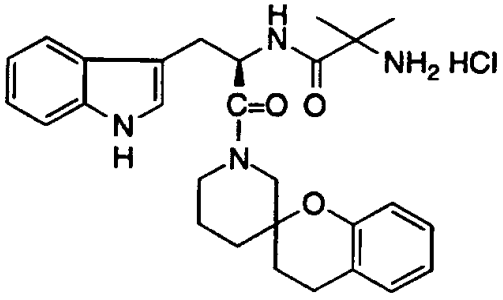
To a solution of the intermediate from the previous step (170 mg, 0.289 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (15 mL) at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the hydrochloric acid and solvents to afford the product (134 mg, 89%). FAB-MS calc. for C28H32N4O4: 488; Found 489 (M+H)

EXAMPLE C2

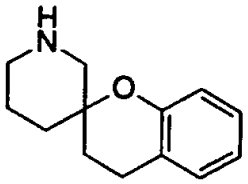


To a stirred solution of the title compound in Example C1 (60 mg, 0.11 mmol) in methanol (10 mL) at 0°C, was added NaBH4 (200 mg) in several portions. The reaction mixture was stirred at 0°C for 2 hours and then quenched by addition of several drops of 3 N HCl. The solution was neutralized by addition of sodium bicarbonate solution. The solution was evaporated to dryness and taken up in 10% methanol in dichloromethane, which was loaded directed to a silica gel flash column and eluted with 10% methanol in dichloromethane to afford the desired compound (51 mg, 91%). FAB-MS calc. for C28H34N4O4: 490; Found 491 (M+H)

EXAMPLE C3

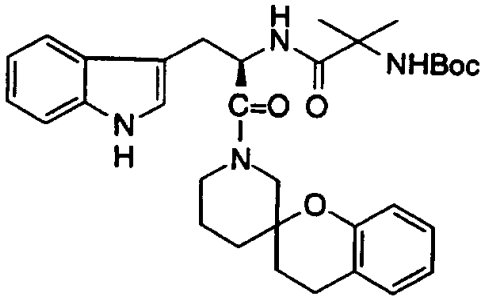


Step A:



To a stirred solution of the intermediate from Example C1 step B (600 mg, 2.4 mmol) in methanol (10 mL) at 0°C, was added NaBH4 (260 mg) in several portions. The reaction mixture was stirred at 0°C for 2 hours and evaporated the dryness. The residue was redissolved in methanol (3 mL) and to which was added concentrated HCl (25 mL) and the resulting solution was stirred at room temperature overnight. The reaction mixture was then evaporated to dryness, and hydrogenated over palladium on carbon (10%, 70 mg) in ethanol (20 mL) under a hydrogen balloon. Filtration through celite gave the desired compound (503 mg, 93%).

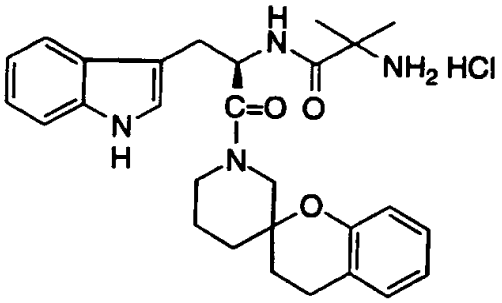
Step C:



To a solution of the intermediate prepared in the previous step (20 mg, 0.1 mmol), Intermediate 1 (1 eq.),and HOBT (1 eq.) in dichloromethane at 0°C, was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a mixture of two diastereomers

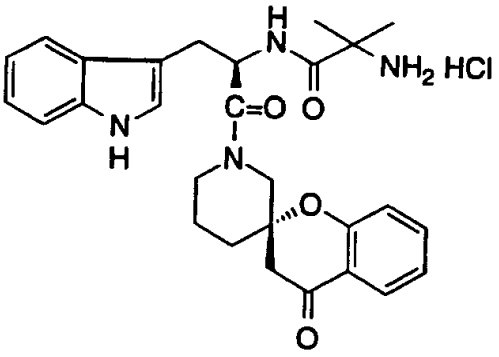
(31.6 mg, 56%). FAB-MS calc. for C33H42N4O5: 574; Found 575 (M+H)

Step D:

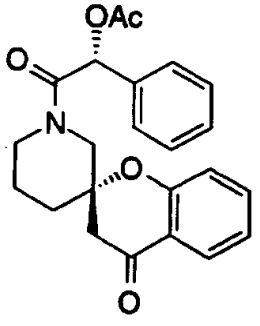


To a solution of the intermediate from the previous step (26.6, 0.046 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (4.5 mL) at 0°C. The reaction was stirred for 1 h, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the hydrochloric acid and solvents to afford the product(22 mg, 93%). FAB-MS calc. for C28H34N4O3: 474; Found 475 (M+H)

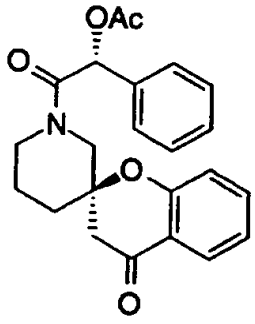
EXAMPLE C4



Step A:



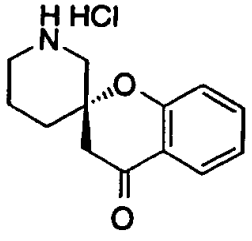
d1 and



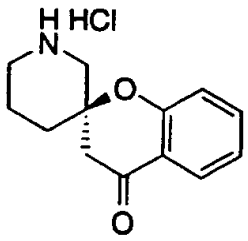
d2

To a stirred mixture of the spiropiperidine hydrochloride (100 mg), (R)-(-)-(O)-acetyl mandelic acid (77 mg, 1 eq.), HOBT (1 eq.) and N-methyl morpholine (1 eq.) in dichloromethane (5 mL) at 0°C, was added EDC (151 mg, 2 eq.). The reaction mixture was stirred at 0°C overnight. The solution was diluted with ethyl acetate and washed with saturated sodium chloride and 3 N HCl, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 40% ethyl acetate in hexane provided two enantiomerically pure compounds. The isomer which came out of the column first was designated as d1 (72.8 mg) and the isomer which came out of the column second as d2 (71.2 mg). The structure of intermediate d2 was determined by x-ray crystallography. Given the absolute stereochemistry of (R) -O-acetylmandelic acid, the stereochemistry at the piperidine 3-position was assigned (R)- in d2.

Step B:



d1 and

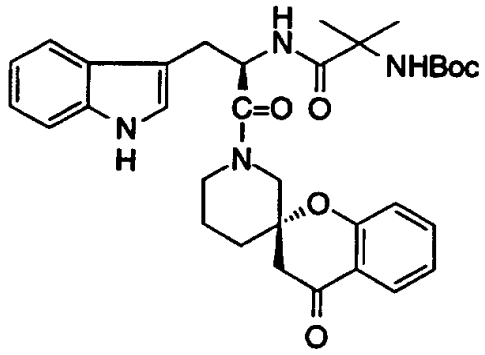


d2

The intermediates from the previous step (d1: 72.8 mg; d2: 71.2 mg) in ethanol (5 mL each) and concentrated HCl (5 mL each) were

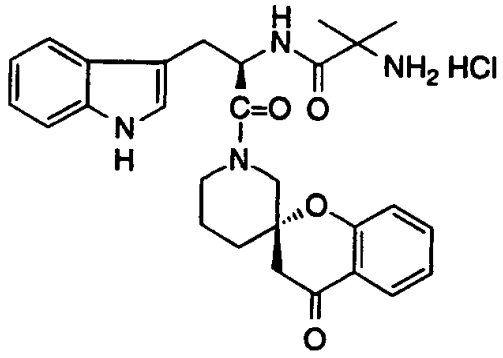
refluxed for one day respectively. The reaction mixtures were evaporated *in vacuo* and the residue was purified by silica gel flash column chromatography eluting first with 10% methanol in dichloromethane and then with 1/10/90 ammonium hydroxide/methanol/chloroform to provide the free amine of the title compounds. The free amines were treated with small amount of hydrogen chloride in methanol to give the salts (d1: 36.6 mg; d2: 37.5 mg). Optical rotation: d1: α°_{D}=-48.5 (methanol, c=0.15 MeOH) ; d2: α°_{D}=+46.9 (methanol, c=0.17 MeOH)

Step C:



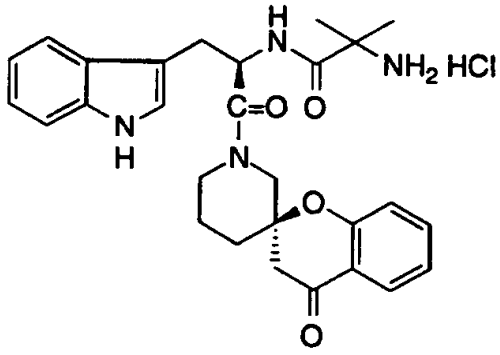
To a solution of the intermediate d1 prepared in the previous step (36.6 mg, 0.144 mmol), Intermediate 1 (112 mg, 2 eq.), HOBT (1 eq.), and NMM (16 µL, 1 eq) in dichloromethane (3 mL) at 0°C, was added EDC (83 mg, 3 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a single enatiomer (112 mg). FAB-MS calc. for C33H40N4O6: 588; Found 589 (M+H)

Step D:

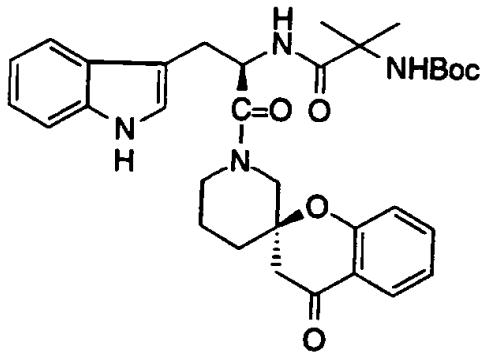


To a solution of the intermediate from the previous step (112 mg) in methanol (3 mL) was added concentrated hydrochloric acid (3 mL) at 0°C. The reaction was stirred for 1 hour. The solution was then evaporated to remove the hydrochloric acid and solvents to afford the product(83.7 mg). FAB-MS calc. for C28H32N4O4: 488; Found 489 (M+H)

EXAMPLE C5

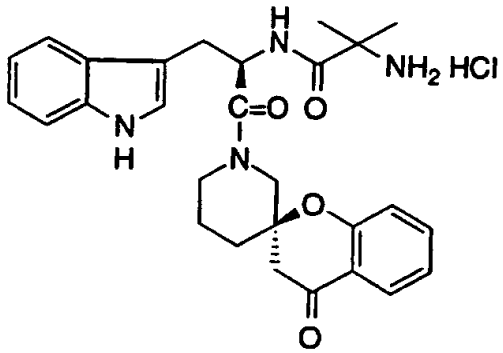


Step A:



To a solution of the intermediate d2 prepared in Example C4 Step B (37.5 mg), Intermediate 1 (115 mg, 2 eq.),and HOBT (1 eq.) , and NMM (16 μL, 1 eq) in dichloromethane (3 mL) at 0°C, was added EDC (85 mg, 3 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a single enatiomer (77.9 mg). FAB-MS calc. for C33H40N4O6: 588; Found 589 (M+H)

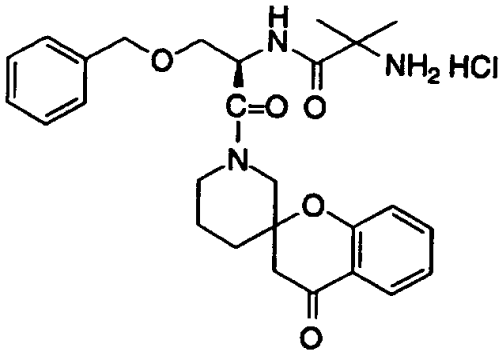
Step B:



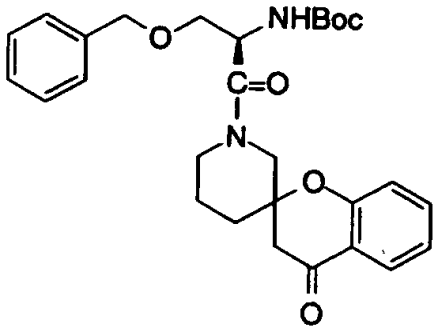
To a solution of the intermediate from the previous step (77.9 mg) in methanol (3 mL) was added concentrated hydrochloric acid (3 mL) at 0°C. The reaction was stirred for 1 hour. The solution was then evaporated to remove the hydrochloric acid and solvents to afford the

product (62.5 mg). FAB-MS calc. for C28H32N4O4: 488; Found 489 (M+H)

EXAMPLE C6

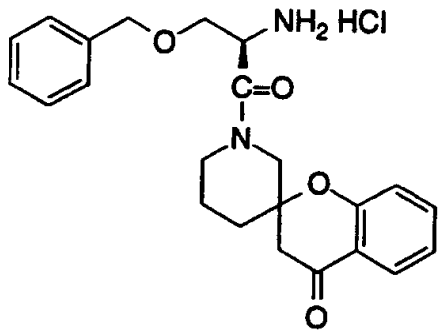


Step A:



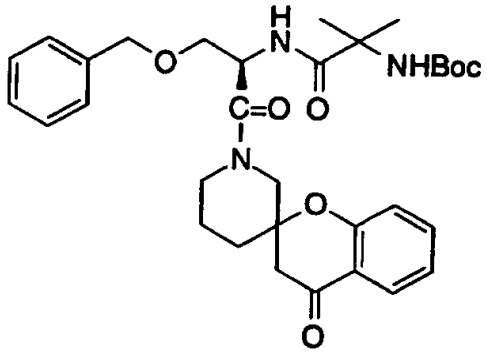
To a solution of the intermediate prepared in Example C1, step B (75 mg, 0.296 mmol), and N-Boc-O-benzyl-D-serine (110 mg, 0.37 mmol.), HOBT (20 mg), and N-methyl morpholine (0.2 mL) in dichloromethane (30 mL) at 0°C was added EDC (170 mg). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (143 mg, 98%). FAB-MS calc. for C28H34N2O6: 494; Found 495 (M+H)

Step B:



To a solution of the intermediate from the previous step (133 mg, 0.269 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (15 mL) at -5°C. The reaction was stirred for 1 hour, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the hydrochloric acid and solvents to afford the product(115 mg, 98%).

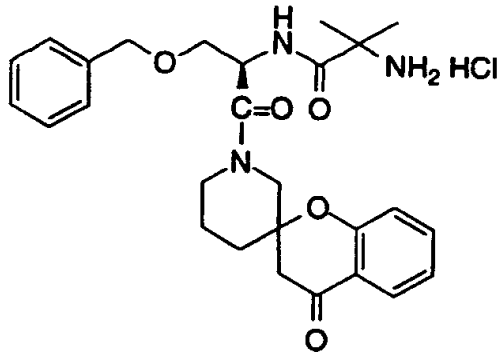
Step C:



To a solution of the intermediate prepared from the previous step (110 mg, 0.255 mmol), N-Boc-alpha-methylalanine (65 mg, 0.319 mmol.), HOBT (20 mg), and N-methyl morpholine (0.1 mL) in dichloromethane (10 mL) at 0°C was added EDC (170 mg). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a mixture of two

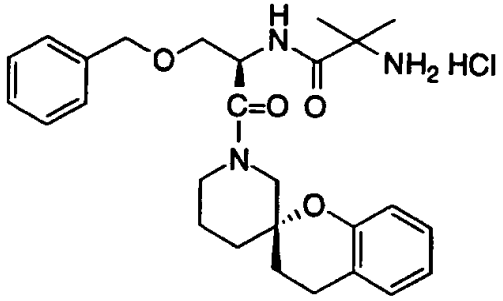
diastereomers (119 mg, 81%). FAB-MS calc. for C32H41N3O7: 579; Found 580 (M+H)

Step D:

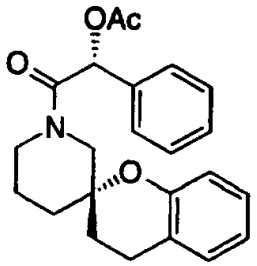


To a solution of the intermediate from the previous step (110 mg, 0.19 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (15 mL) at 0°C. The reaction was stirred for 45 minutes until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the hydrochloric acid and solvents to afford the product (95.8 mg, 98%). FAB-MS calc. for C27H33N3O5: 479; Found 480 (M+H)

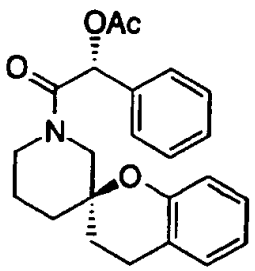
EXAMPLE C7



Step A:



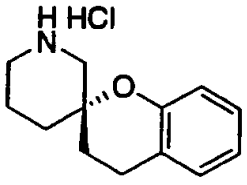
d1 and



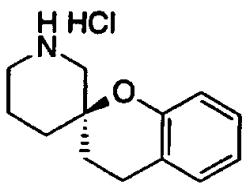
d2

To a stirred mixture of the intermediate from Example C3 step A (400 mg, 1.67 mmol), (R)-(-)-(O)-acetyl mandelic acid (325 mg, 1.67 mmol), HOBT (226 mg, 1.67 mmol) and N-methyl morpholine (103 mg) in dichloromethane (15 mL) at 0°C, was added EDC (151 mg, 2 eq.). The reaction mixture was stirred at 0°C overnight. The solution was diluted with ethyl acetate and washed with saturated sodium chloride and 3 N HCl, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 50% ethyl acetate in hexane provided two enantiomerically pure compounds. The isomer which came out of the column first was designated as d1 (275 mg) and the isomer which came out of the column second as d2 (257 mg). The structure of these intermediates were assigned based on NMR similarities with the intermediates from Example C4 Step A. Intermediate d1 has S stereochemistry at the spiro center, while intermediate d2 has R stereochemistry at the spiro center.

Step B:



d1 and

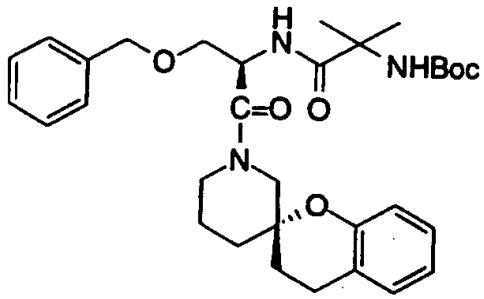


d2

The intermediates from the previous step (d1: 275 mg; d2: 257 mg) in ethanol (20 mL each) and concentrated HCl (20 mL each) were refluxed for one day respectively. The reaction mixtures were

evaporated *in vacuo* and the residue was purified by silica gel flash column chromatography eluting first with 10% methanol in dichloromethane and then with 0.7:7:93 ammonium hydroxide:methanol:chloroform to provide the free amine of the title compounds (d1: 136 mg; d2: 96 mg).

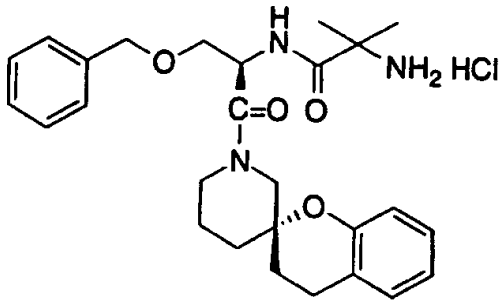
Step C:



To a solution of the intermediate d1 prepared in the previous step (106 mg, 0.52 mmol), Intermediate 2 (218 mg, 0.57 mmol),and HOBT (70 mg, 0.52 mmol) in dichloromethane (20 mL) at 0°C, was added EDC (83 mg, 3 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC provided the compound as a single enatiomer (225 mg, 77%).

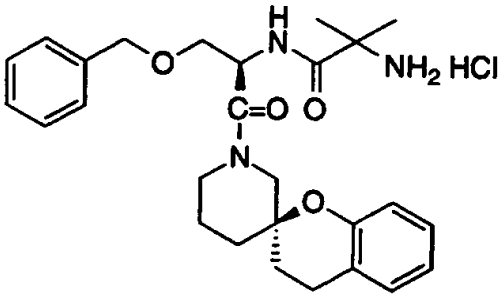
FAB-MS calc. for C32H43N3O6: 565; Found 566 (M+H)

Step D:

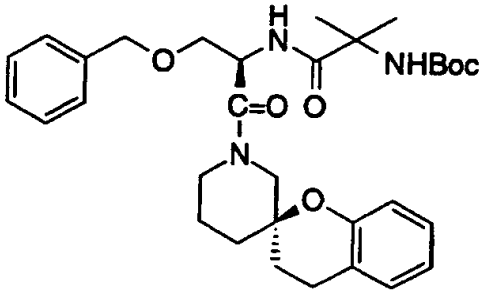


To a solution of the intermediate from the previous step (220 mg, 0.39 mmol) in ethyl acetate (5 mL) was bubbled HCl gas at 0°C for 1 minute. The reaction was stirred for 50 minutes and then evaporated to remove the HCl and solvents to afford the product(190 mg, 98%). FAB-MS calc. for C27H35N3O4: 465; Found 466 (M+H)

EXAMPLE C8

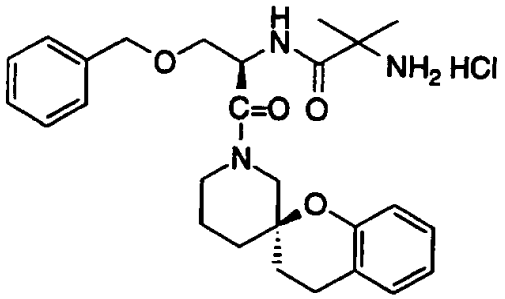


Step A:



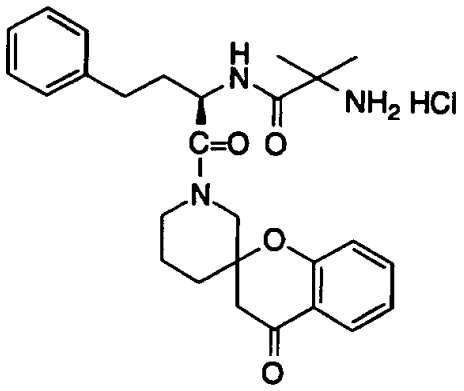
To a solution of the intermediate d2 prepared in Example C7 Step B (86 mg, 0.423 mmol), Intermediate 2 (177 mg, 0.465 mmol), and HOBT (57 mg, 0.423 mmol) in dichloromethane (20 mL) at 0°C, was added EDC (178 mg, 0.93 mmol). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC provided the compound as a single enatiomer (195 mg, 82%). FAB-MS calc. for C32H43N3O6: 565; Found 566 (M+H)

Step B:

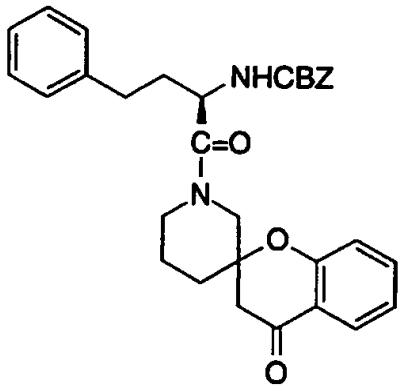


To a solution of the intermediate from the previous step (190 mg, 0.336 mmol) in ethyl acetate (5 mL) was bubbled HCl gas at 0°C for 1 minute. The reaction was stirred for 50 minutes and then evaporated to remove the HCl and solvents to afford the product(166 mg, 98%). FAB-MS calc. for C27H35N3O4: 465; Found 466 (M+H)

EXAMPLE C9

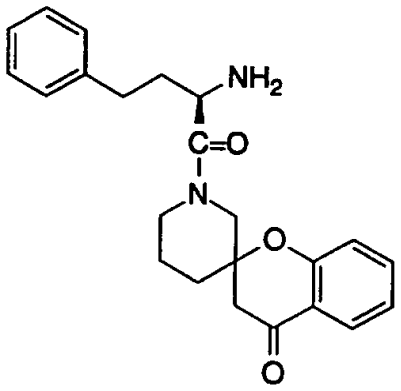


Step A:



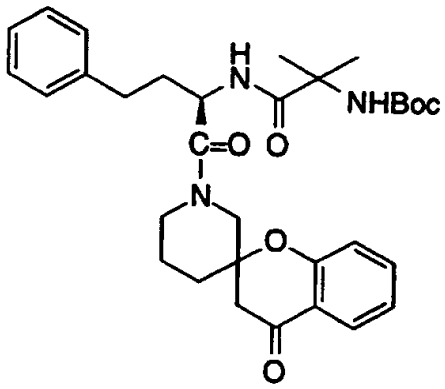
To a solution of the intermediate prepared Example C1, step B (75 mg, 0.296 mmol), and N-Cbz-D-homophenylalanine (115 mg, 0.37 mmol.), HOBT (20 mg), and N-methyl morpholine (0.2 mL) in dichloromethane (30 mL) at 0°C, was added EDC (170 mg). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 50% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (148.6 mg, 98%). FAB-MS calc. for C31H32N2O5: 512; Found 513 (M+H)

Step D:



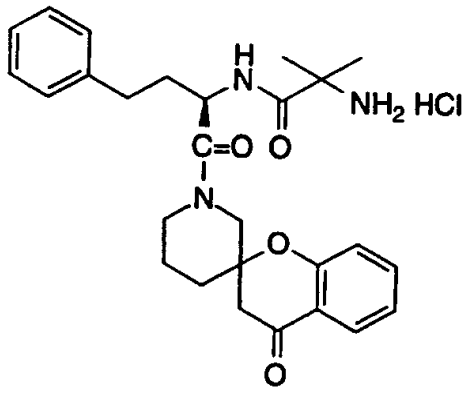
A suspension of the intermediate obtained from the previous step (135 mg, 0.263 mmol) and palladium on carbon (10%, 60 mg) in ethanol (20 mL) was stirred under a hydrogen balloon for 1.5 hours. The resulting mixture was filtered through celite and the solution was evaporated to give the desired compound (87 mg, 87%).

Step C:



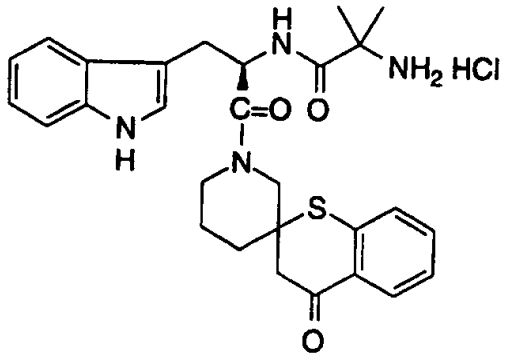
To a solution of the intermediate prepared from the previous step (76 mg, 0.2 mmol), N-Boc-alpha-methylalanine (51 mg, 0.251 mmol.), and HOBT (20 mg) in dichloromethane (10 mL) at 0°C was added EDC (96 mg). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (86 mg, 76%). FAB-MS calc. for C32H41N3O6: 563; Found 564 (M+H)

Step D:

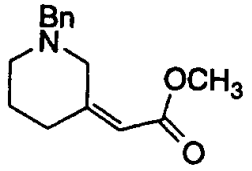


To a solution of the intermediate from the previous step (75 mg, 0.13 mmol) in methanol (10 mL) was added concentrated hydrochloric acid (15 mL) at 0°C. The reaction was stirred for 45 minutes until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the hydrochloric acid and solvents to afford the product (67 mg, 99%). FAB-MS calc. for C27H33N3O4: 463; Found 464 (M+H)

EXAMPLE C10

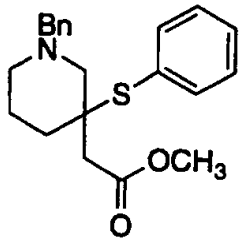


Step A:



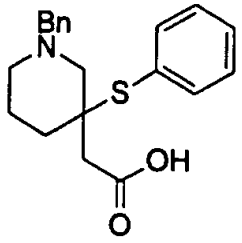
To a suspension of sodium hydride (0.63g, 26.4 mmol) in THF (35 mL) was added the methyl diethylphosphonoacetate (5.6g, 26.4 mmol) with cooling to maintain the temperature below 30°C. The solution was stirred 15 min. which became clear. The N-benzyl-3-piperidinone was added while still maintaining the temp. below 30°C and after the addition was complete, warming the reaction mixture to 60°C and stirring 15 min. The mixture was cooled to room temperature. and the mixture filtered. The filtrate was concentrated and the residue chromatographed (SiO2, 1:1 hexane/EtOAc) to provide 5.4g of the title compound.

Step B:



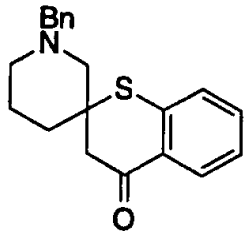
To a solution of the alkene (0.5g, 2.04 mmol) and potassium carbonate (0.13g, 1.26 mmol) in THF (10 mL) was added thiophenol (0.23 mL, 2.24 mmol) and the mixture refluxed 16 hr. The reaction was concentrated to dryness and partitioned between EtOAc/2N HCl. The aqueous portion was extracted with EtOAc, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford 0.54g of the title compound.
CI-MS calc. for C21H35NO2S: 355; Found 356 (M+H)

Step C:



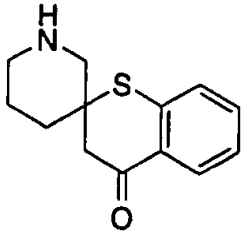
To a solution of the thioether (2.7g, 8.44 mmol) in 1:1:3 H_2O/THF/MeOH (20 mL) was added lithium hydroxide (2.0g, 42.2 mmol) and the reaction mixture stirred 4 hr. The reaction mixture was concentrated and then partitioned between EtOAc/2N HCl. The aqueous portion was adjusted to pH 7 with NaHCO3 and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to provide 0.75g of the title compound.
CI-MS calc. for C20H23NO2S: 341; Found 342 (M+H)

Step D:



To a solution of the carboxylic acid from the previous step (0.41g, 1.20 mmol) in CH_2Cl_2 (10 mL) and DMF (.25 mL) at 10°C was added oxalyl chloride (2.5 mL, 4.10 mmol). Triflic acid was added and the mixture warmed to room temperature. while stirring 3 hr. The reaction mixture was poured into H_2O (25 mL) and the aqueous portion extracted with EtOAc. All the organic portions were combined and dried over $MgSO_4$, filtered, evaporated and purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to yield the desired compound (0.26 g, 69%).
CI-MS calc. for C20H21NOS: 323; Found 324 (M+H)

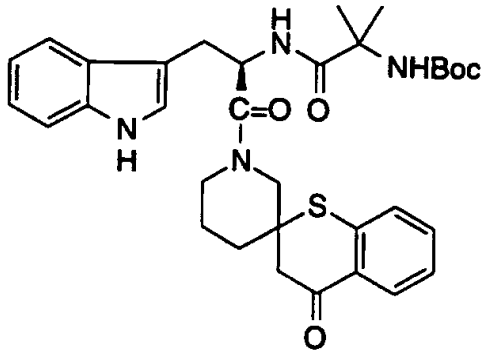
Step E:



To a stirred solution of the intermediate obtained from previous step (3.5 g, 0.0114 mol) in dichloroethane was added α-chloroethyl chloroformate (ACE-Cl, 1.79 g,0.0125 mol). The resulting solution was refluxed for 30 minutes and evaporated to dryness. The residue was dissolved in methanol (50 mL) and refluxed for 30 minutes. The solution was concentrated to 1/4 of the initial volume the resulting crystals were collected (.545 g). The mother liquor was poured into 0.3 N HCl and extracted with ethyl acetate. The aqueous solution was adjusted to pH 10 with 2 N NaOH, the suspension was extracted with ethyl acetate and then with chloroform. Purification by silica gel chromatography eluting with 1:9 MeOH/chloroform gave the compound (0.185 g).

CI-MS calc. for C13H15NOS: 233; Found 234 (M+H)

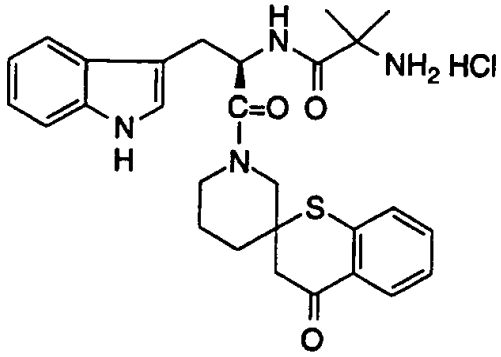
Step F:



To a solution of the intermediate prepared in the previous step (35 mg, 0.43 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by silica gel chromatography eluting with 70% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (81 mg, 98%).

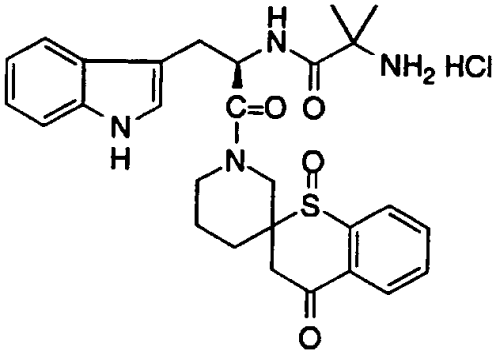
ESI-MS calc. for C33H40N4O5S: 604; Found 605 (M+H)

Step G:

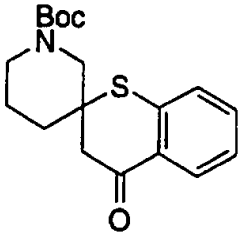


To a solution of the intermediate from the previous step (83 mg, 0.128 mmol) in ethyl acetate (10 mL) was bubbled HCl gas for 3 minutes at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then evaporated to afford the product (90 mg, 89%). ESI-MS calc. for C28H32N4O3S: 504; Found 505 (M+H)

EXAMPLE C11

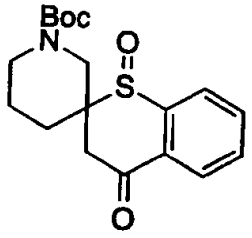


Step A:

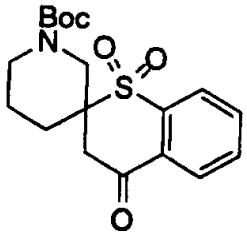


To a stirred solution of the intermediate from Example C10 step E (0.14g, 0.45 mmol) in CH_2Cl_2 (1.2 mL) at 0°C was added di-t-butyl-dicarbonate (0.11g, 0.49 mmol). After 2 hr. the reaction was poured into EtOAc and washed with 2N HCl, saturated Na_2CO_3, brine and dried over $MgSO_4$. The solvent was removed and the resulting residue chromatographed (SiO_2, 9:1 hexane/EtOAc) to provide 125 mg of the title compound. CI-MS calc. for C18H23NO3S: 333; Found 334 (M+H)

Step B:

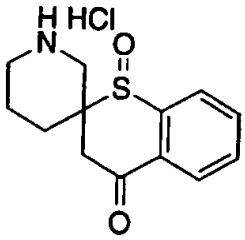


and



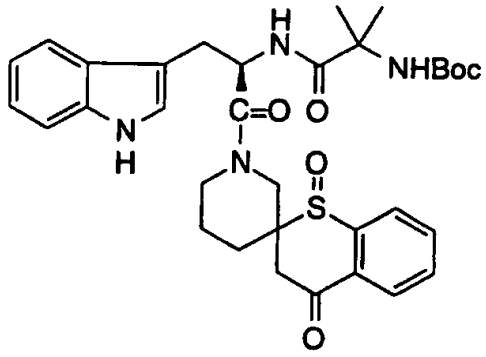
To a stirred solution of the spiro[3H-4-oxo-1-benzothiopyran-2,3'-piperidine] (0.12g, 0.33 mmol) in MeOH (5.0 mL) Oxone (2 Eq) was added in one portion. the reaction mixture was stirred 6 hr., then poured into EtOAc and washed with water, brine and dried over $MgSO_4$. The solvent was removed and the resulting residue chromatographed (SiO_2, 9:1 CH_2Cl_2/EtOAc) to provide 85 mg (71%) of the sulfone and 30 mg (26%) of the sulfoxide. sulfoxide: CI-MS calc. for C18H23NO4S: 349; Found 350 (M+H); sulfone: CI-MS calc. for C18H23NO5S: 365; Found 366 (M+H)

Step B:



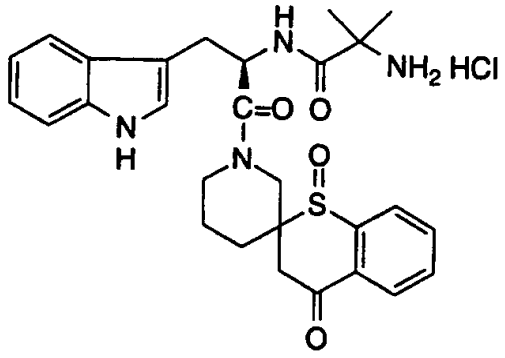
To a solution of the intermediate from the previous step (30 mg, 0.086 mmol) in ethyl acetate (25 mL) was bubbled HCl gas for 3 minutes at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then evaporated to afford the product (29 mg, 95%). CI-MS calc. for C13H15NO2S: 249; Found 250 (M+H)

Step C:



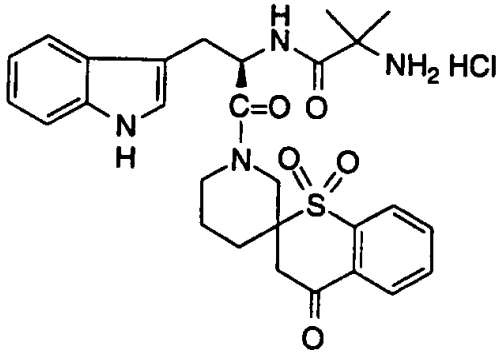
To a solution of the sulfoxide prepared in the previous step (23 mg, 0.081 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by silica gel chromatography eluting with 70% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (30 mg, 50%). ESI-MS calc. for C33H40N4O6S: 620; Found 621 (M+H)

Step D:

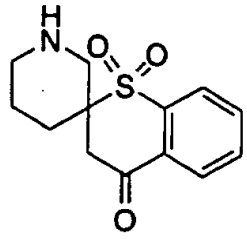


To a solution of the intermediate from the previous step (20 mg, 0.04 mmol) in ethyl acetate (5 mL) was bubbled HCl gas for 3 minutes at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then evaporated to afford the product (17 mg, 98%). ESI-MS calc. for C28H32N4O4S: 520; Found 521 (M+H)

EXAMPLE C12

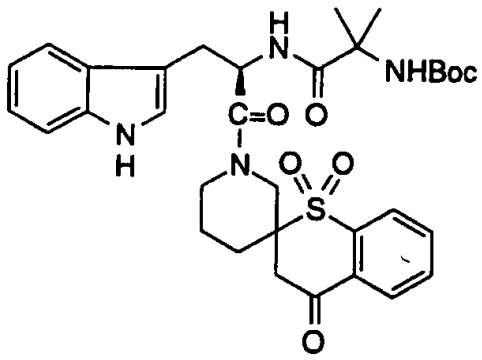


Step A:



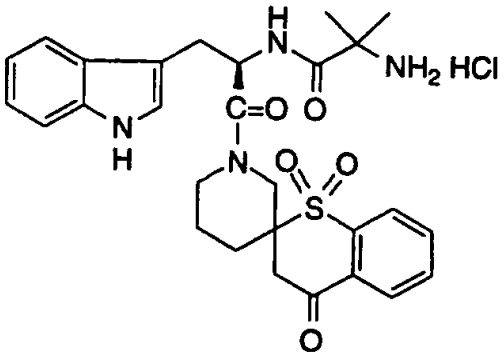
To a solution of the sulfone from Example C11 Step B (38 mg, 0.104 mmol) in ethyl acetate (5 mL) was bubbled HCl gas for 3 minutes at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then evaporated to afford the product (23 mg, 85%). CI-MS calc. for C13H15NO3S: 265; Found 266 (M+H)

Step B:



To a solution of the sulfone prepared in the previous step (36 mg, 0.119 mmol), and Intermediate 1 (1 eq.), HOBT (1 eq.), N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by silica gel chromatography eluting with 70% ethyl acetate in hexane provided the compound as a mixture of two diastereomers (35 mg, 45%). ESI-MS calc. for C33H40N4O7S: 636; Found 637 (M+H)

Step C:

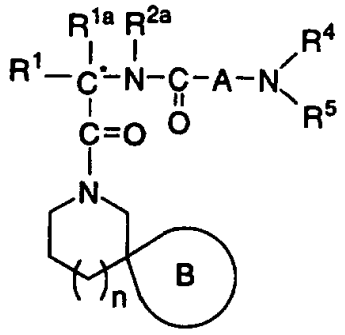


To a solution of the intermediate from the previous step (15 mg, 0.05 mmol) in ethyl acetate (5 mL) was bubbled HCl gas for 3 minutes at 0°C. The reaction was stirred for 25 minutes until TLC analysis indicated that the reaction was complete. The solution was then evaporated to afford the product (12 mg, 89%). ESI-MS calc. for C28H32N4O5S: 537; Found 538 (M+H)

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

R1 is selected from the group consisting of:
C_1-C_{10} alkyl, aryl, aryl (C_1-C_6 alkyl),
(C_3-C_7 cycloalkyl)(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
aryl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and
(C_3-C_7 cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
where K is -O-, -S(O)$_m$-, -N(R^2)C(O)-, -C(O)N(R^2)-, -OC(O)-, -C(O)O-,
-CR^2=CR^2-, or -C≡C-, where R^2 and alkyl may be further substituted by
1 to 9 halogen, S(O)$_m$$R^{2a}$, 1 to 3 of O$R^{2a}$ or C(O)OR^{2a}, and aryl is
selected from: phenyl, naphthyl, quinolinyl, isoquinolinyl, indolyl,
azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and
benzimidazolyl, and where the aryl is unsubstituted or substituted with a
substitutent selected from: 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to
2 of -OR^2, methylenedioxy, -S(O)$_m$$R^2$, 1 to 2 of -$CF_3$, -$OCF_3$, nitro,
-N(R^2)C(O)(R^2), -C(O)OR^2, -C(O)N(R^2)(R^2), -1H-tetrazol-5-yl,
-SO_2N(R^2)(R^2), -N(R^2)SO_2 phenyl, or -N(R^2)$SO_2$$R^2$;

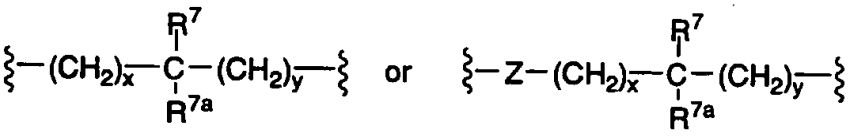
R1a is selected from hydrogen and C_1-C_6 alkyl;

R^2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they optionally are joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

R^{2a} is selected from hydrogen and C_1-C_6 alkyl;

R^4 and R^5 are independently hydrogen, unsubsubstituted C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituent is selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenyloxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl), or R^4 and R^5 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, -O-, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

A is:



where x and y are independently 0, 1, 2 or 3;

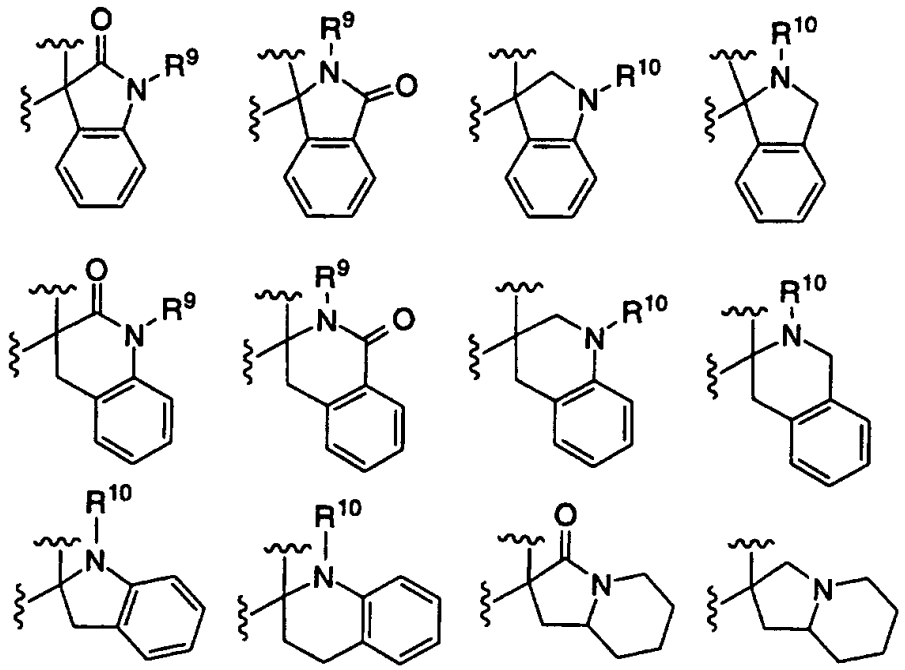
Z is $-N(R^{6a})-$ or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl and the C_1-C_6 alkyl is optionally joined to R^4 or R^5 to form a five, six or seven membered ring;

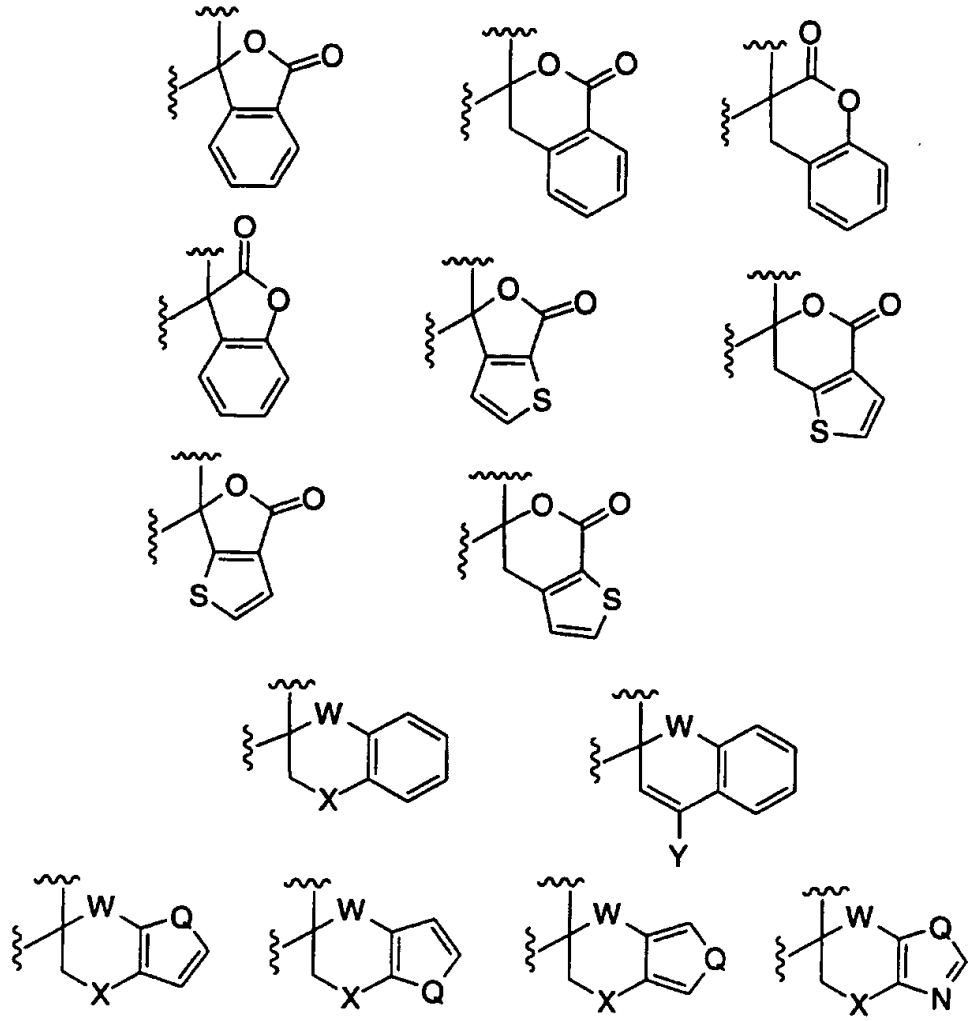
R^7 and R^{7a} are independently hydrogen, unsubstituted C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3-C_7 cycloalkyl, $-N(R^2)(R^2)$, and $-C(O)N(R^2)(R^2)$; or R^7 and R^{7a} independently may be joined to one or both of R^4 and R^5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^7 or R^{7a} groups, wherein

the bridge contains 1 to 5 carbons atoms; or R^7 and R^{7a} are optionally joined to one another to form a C3-C7 cycloalkyl;

B is selected from the group consisting of:

5





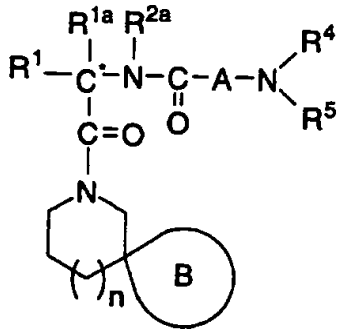
where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
where W is selected from -O- and -S-,
Q is selected from -O-, -S- and -$N(R^2)$-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

m is 0, 1, or 2; and
n is 0 or 1;
and the hydroxy acid open lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

2. The compound of Claim 1 of the formula:



wherein:

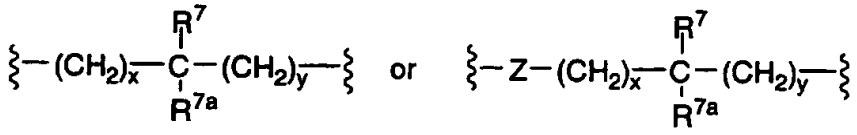
R^1 is selected from the group consisting of:

C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl (C_1-C_4 alkyl)-, (C_1-C_4 alkyl)-K-(C_1-C_2 alkyl)-, aryl (C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, where K is -O-, -S(O)m-, -OC(O)-, or -C(O)O-, and the alkyl groups may be further substituted by 1 to 7 halogen, -S(O)$_m$$R^2$, 1 to 3 -O$R^2$ or -C(O)OR^2, and aryl is selected from: phenyl, naphthyl, quinolinyl, isoquinolinyl, indolyl, pyridyl, benzimidazolyl, azaindolyl, benzothienyl and benzofuranyl and where the aryl is unsubstituted or substituted with a substitutent selected from: 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -S(O)$_m$$R^2$, and -C(O)O$R^2$;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_4-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_4 alkyl;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituent is selected from: 1 to 5 halo, 1 to 3 hydroxyl, -S(O)m (C_1-C_6 alkyl) and phenyl;

A is:

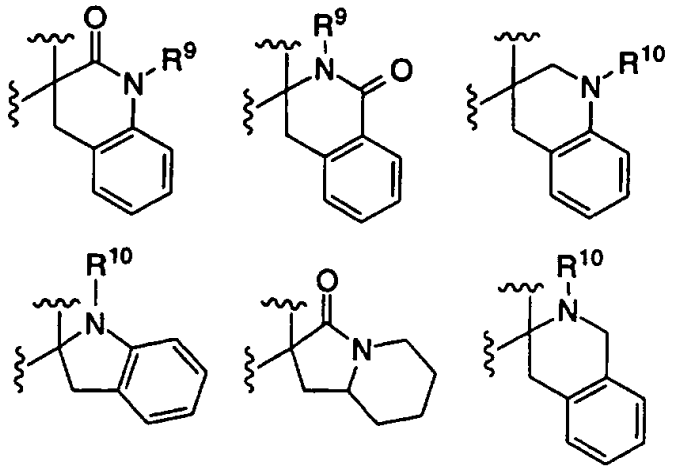


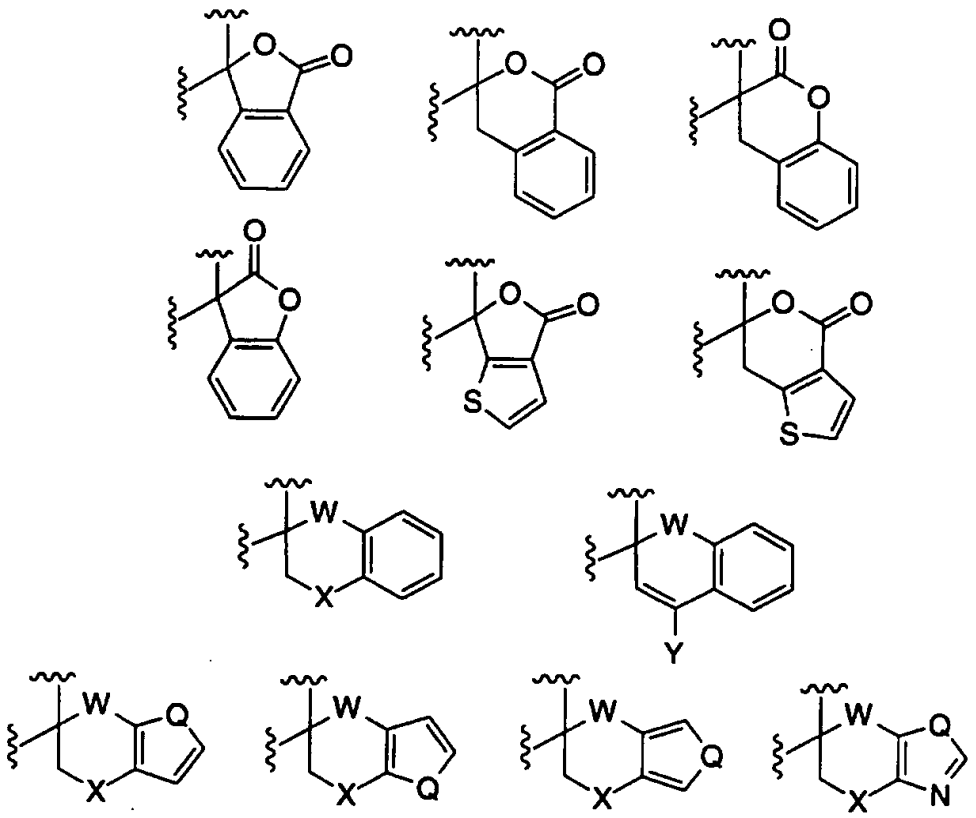
where x and y are independently 0, 1 or 2;

Z is -NR6a- or -O-, where R6a is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R^4 or R^5 to form a six or seven membered ring;

R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, OR^2, $S(O)mR^2$, $C(O)OR^2$, C_5-C_7 cycloalkyl, $-N(R^2)(R^2)$, and $-C(O)N(R^2)(R^2)$; or R^7 and R^{7a} can independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 and R^{7a} can be joined to one another to form a C_3 cycloalkyl;

B is selected from the group consisting of:





where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

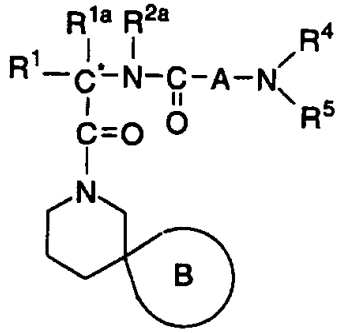
R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl,

where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
where W is selected from -O- and -S-,
Q is selected from -O-, -S- and -$N(R^2)$-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, $CH\text{-}O\text{-}C(O)R^2$, $CH\text{-}O\text{-}C(O)N(R^2)(R^2)$, $CH\text{-}C(O)OR^2$ and $CH\text{-}C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

m is 0, 1, or 2; and
n is 0 or 1;
and the hydroxy acid opens lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

3. The compound of Claim 1 of the formula:



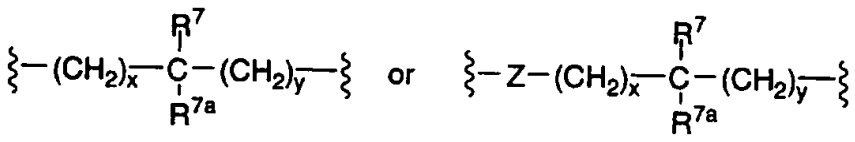
wherein:

R^1 is selected from the group consisting of: C_1-C_{10} alkyl, aryl (C_1-C_3 alkyl)-, (C_3-C_7 cycloalkyl)(C_1-C_3 alkyl)-, and aryl (C_0-C_1 alkyl)-K-(C_1-C_2 alkyl)-, where K is O or $S(O)_m$ and the aryl is selected from: phenyl, pyridyl, naphthyl, quinolinyl, isoquinolinyl, indolyl, azaindolyl, benzothienyl, and benzimidazolyl and where the aryl is unsubstituted or substituted with a substitutent selected from: 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or $C(O)OR^2$;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a} where R^{3a} is hydrogen, or C_1-C_3 alkyl;

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, or substituted C_1-C_3 alkyl where the substituent is 1 to 2 hydroxyl;

A is:

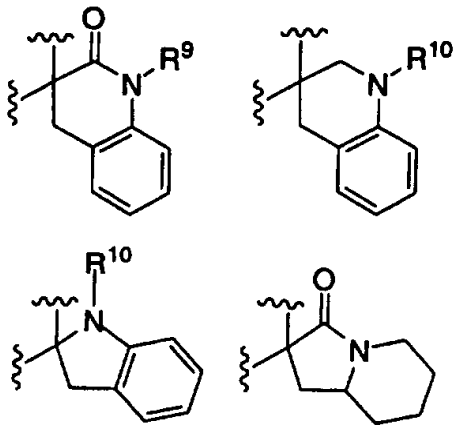


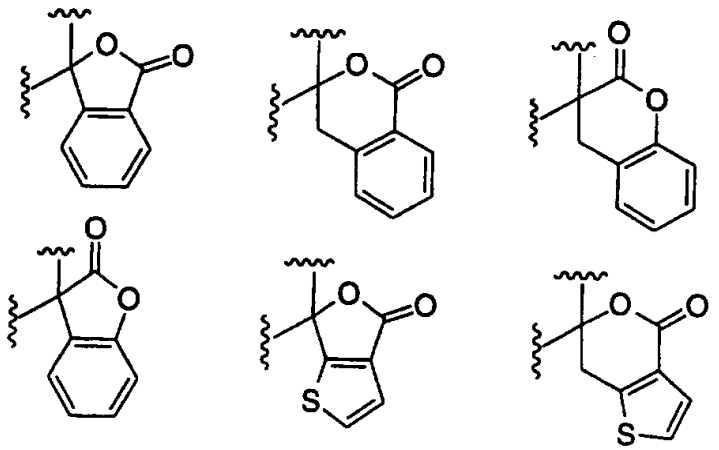
where x and y are independantly 0, 1, or 2;

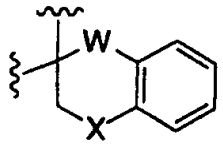
Z is -N(R6a)- or -O-, where R6a is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R4 or R5 to form a six or seven membered ring;

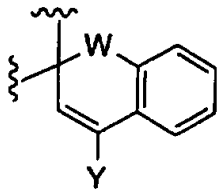
R7 and R7a are independently hydrogen, C_1-C_6 alkyl, phenyl, substituted C_1-C_6 alkyl where the substitutent is selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR2, and -S(O)mR2, or R7 and R7a can independently be joined to one of R4 or R5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R7 or R7a groups to form 5 or 6 membered rings; or R7 or R7a can be joined to one another to form a C_3-C_6 cycloalkyl;

B is selected from the group consisting of:







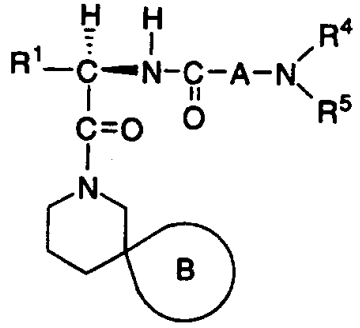


where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);

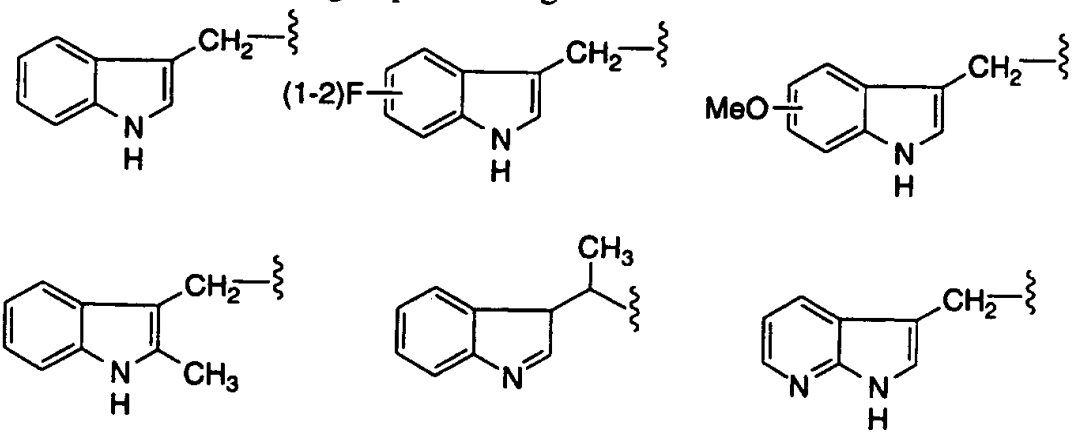
R9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR2, -C(O)OR2, -C(O)N(R2)(R2), nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_m$R2, and 1H-tetrazol-5-yl;
R10 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -C(O)R2, -C(O)$(CH_2)_t$aryl, -C(O)N(R2)(R2), -C(O)N(R2)$(CH_2)_t$aryl, -C(O)OR2, -C(O)$(CH_2)_t$aryl, -SO_2R2, -$SO_2(CH_2)_t$aryl, -SO_2N(R2)(R2), and -SO_2N(R2)$(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, 1-H-tetrazol-5-yl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, oxadiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -CH(OR2)-, CH-O-C(O)R2, CH-O-C(O)N(R2)(R2), CH-C(O)OR2 and CH-C(O)N(R2)(R2),
Y is selected from: hydrogen, -C(O)OR2 and -C(O)N(R2)(R2), and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen; -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);

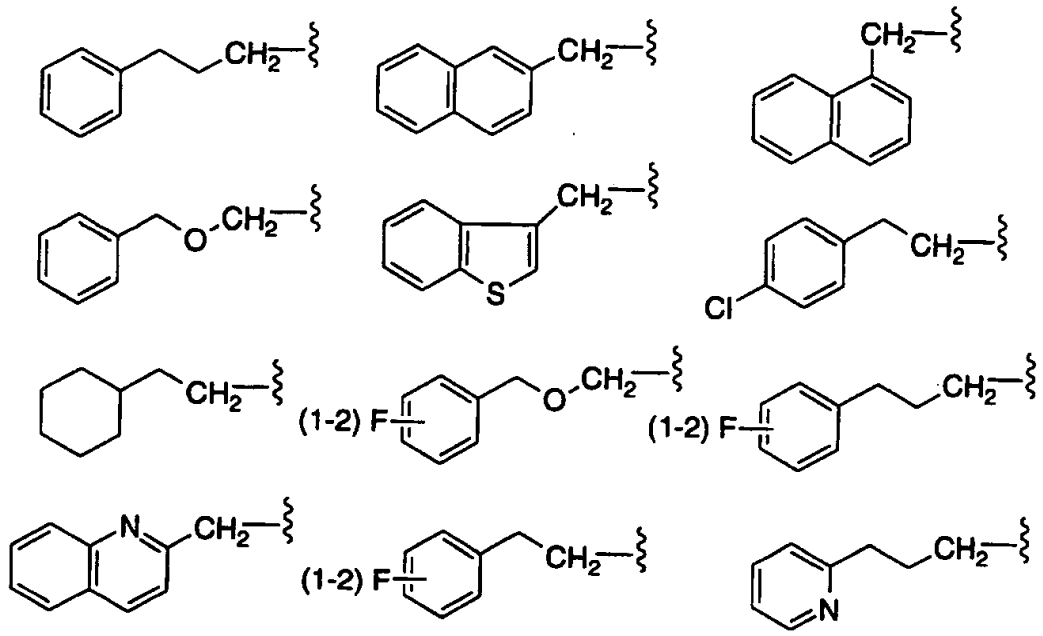
m is 0, 1, or 2; and
and the hydroxy acid open lactone forms;
and pharmaceutically acceptable salts and individual diastereomers thereof.

4. The compound of Claim 1 of the formula:



wherein:
R1 is selected from the group consisting of:

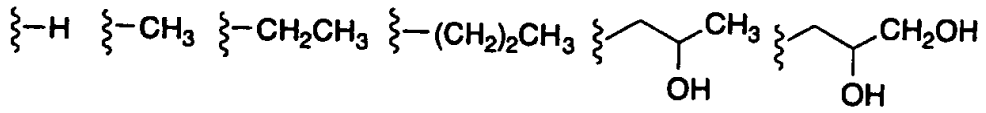




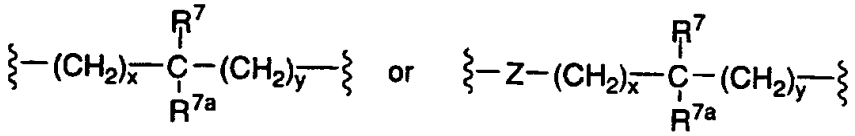
or their regioisomers where not specified;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR_{3a} where R_{3a} is hydrogen, or C_1-C_2 alkyl;

R^4 and R^5 are independently selected from the group consisting of:



A is:

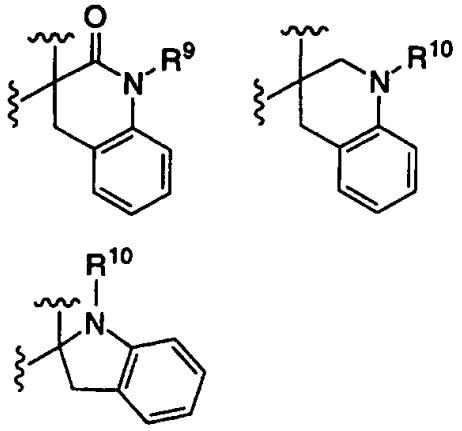


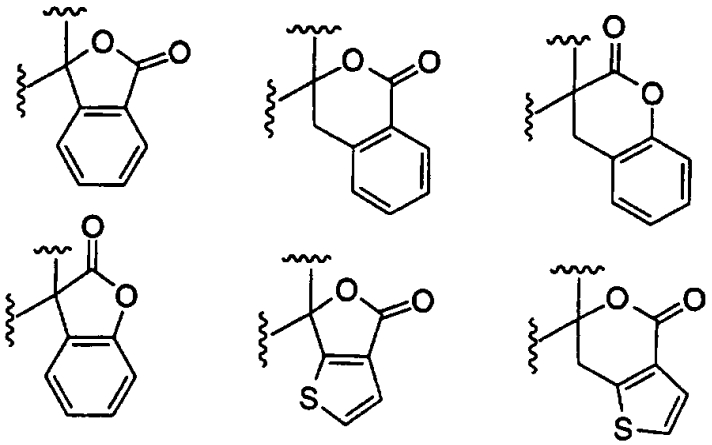
where x and y are independently 0, 1, or 2;

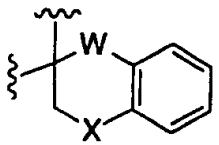
Z is -(NR6a)- or -O-, where R6a is hydrogen or C_1-C_3 alkyl and the C_1-C_3 alkyl is optionally joined to R4 or R5 to form a six membered ring;

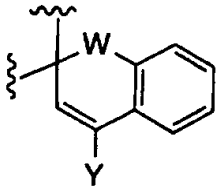
R7 and R7a are independently hydrogen, unsubstituted C_1-C_6 alkyl or substituted C_1-C_6 alkyl wherein the substituent is selected from: phenyl, naphthyl and indolyl; or R7 and R7a independently may be joined to one of R4 or R5 to form an alkylene bridge between the terminal nitrogen and the alkyl portions of R7 or R7a to form a 5 or 6 membered ring;

B is selected from the group consisting of:









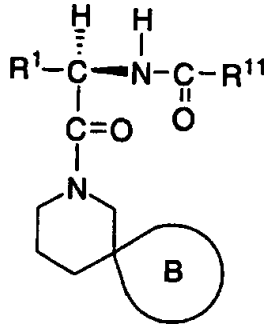
where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);

R9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, indolyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR2, -C(O)OR2, -C(O)N(R2)(R2), nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_m$R2, and 1H-tetrazol-5-yl;

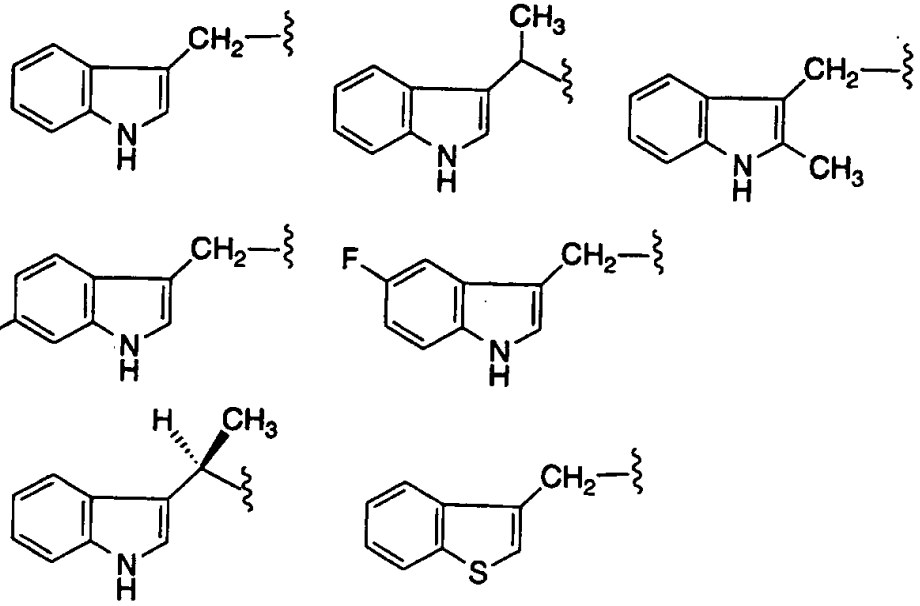
R10 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -C(O)R2, -C(O)$(CH_2)_t$aryl, -C(O)N(R2)(R2), -C(O)N(R2)$(CH_2)_t$aryl, -C(O)OR2, -C(O)$(CH_2)_t$aryl, -SO_2R2, -$SO_2(CH_2)_t$aryl, -SO_2N(R2)(R2), and -SO_2N(R2)$(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, thienyl, indolyl, quinolinyl, and isoquinolinyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -CH(OR2)-, CH-O-C(O)R2, CH-O-C(O)N(R2)(R2), CH-C(O)OR2 and CH-C(O)N(R2)(R2),
Y is selected from: hydrogen, -C(O)OR2 and -C(O)N(R2)(R2), and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R2, -OR2, -N(R2)(R2), -C(O)OR2, and -C(O)N(R2)(R2);

m is 0, 1 or 2;
and the hydroxyacid open lactone forms;
and pharmaceutically acceptable salts and individual diasteromers thereof.

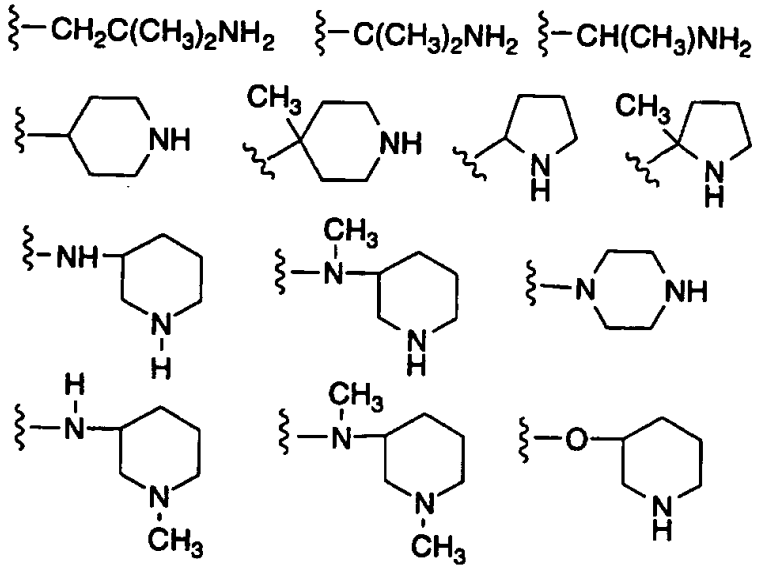
5. A compound of the formula:



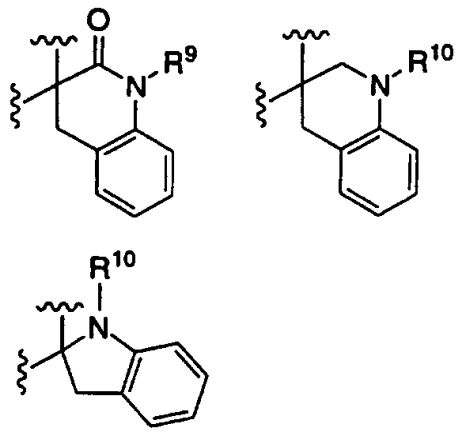
wherein:
R1 is selected from the group consisting of:

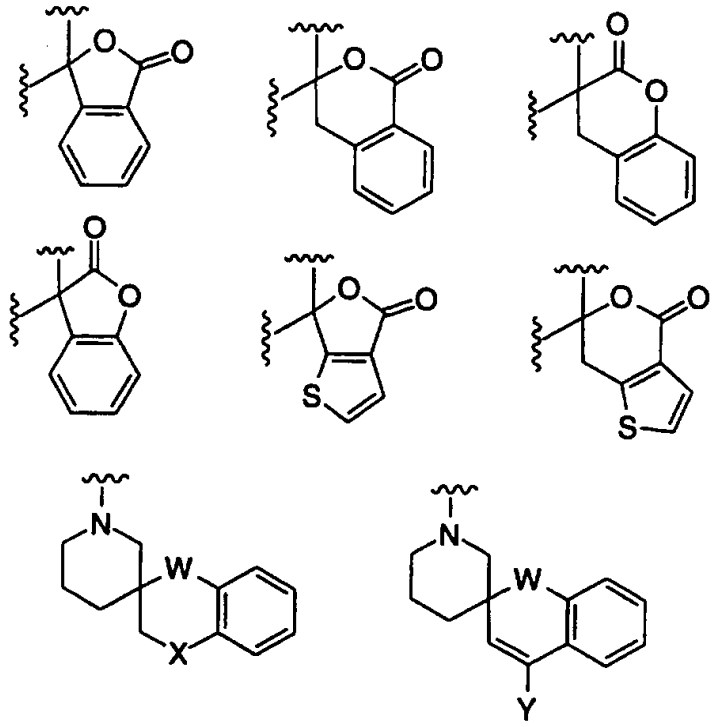


R11 is selected from the group consisting of:



B is selected from the group consisting of:





where either ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

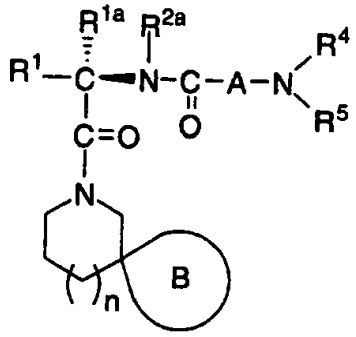
R^9 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, and -$(CH_2)_t$aryl, where t is 0, 1, or 2, and aryl is selected from: phenyl, naphthyl, pyridyl, and thiazolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, and 1H-tetrazol-5-yl;

R^{10} is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, -$(CH_2)_t$aryl, -$C(O)R^2$, -$C(O)(CH_2)_t$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_t$aryl, -$C(O)OR^2$, -$C(O)(CH_2)_t$aryl, -SO_2R^2, -$SO_2(CH_2)_t$aryl, -$SO_2N(R^2)(R^2)$, and -$SO_2N(R^2)(CH_2)_t$aryl, where t is 0, 1, or 2, and where aryl is selected from: phenyl, naphthyl, thiazolyl, pyridyl, and indolyl, where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;
where W is selected from -O- and -S-,
X is selected from the group consisting of: -CH_2-, -C(O)-, -$CH(OR^2)$-, CH-O-$C(O)R^2$, CH-O-$C(O)N(R^2)(R^2)$, CH-$C(O)OR^2$ and CH-$C(O)N(R^2)(R^2)$,
Y is selected from: hydrogen, -$C(O)OR^2$ and -$C(O)N(R^2)(R^2)$, and where the benzo ring is unsubstituted or substituted with a substitutent selected from the group consisting of: 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, and -$C(O)N(R^2)(R^2)$;

and the hydroxyacid open lactone forms;

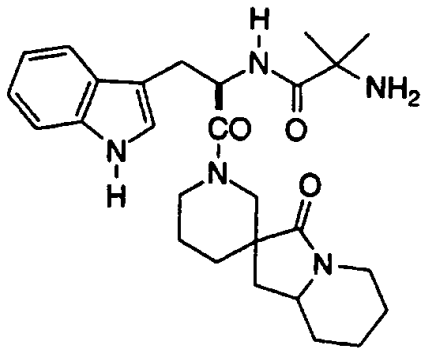
and pharmaceutically acceptable salts and individual diasteromers thereof.

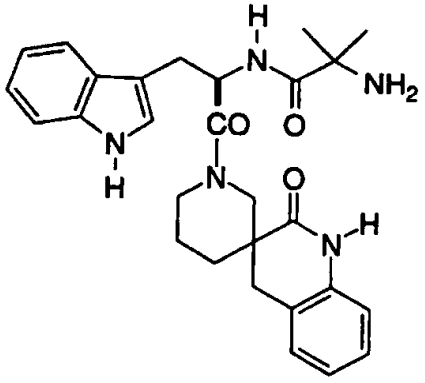
6. The stereospecifically defined compound of Claim 1 of the formula:

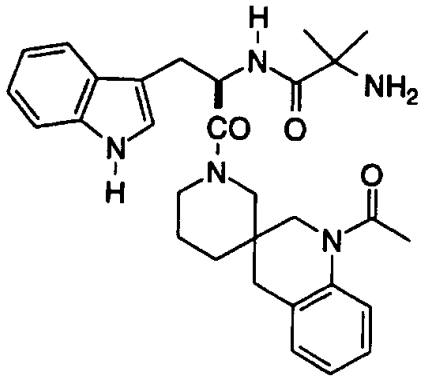


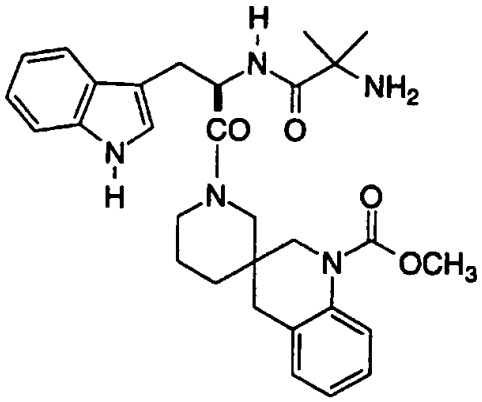
wherein R1, R1a, R2a, R4, R5, A, B and n are as defined in Claim 1.

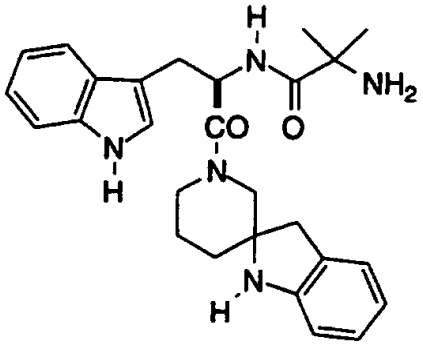
7. A compound which is selected from the group consisting of:

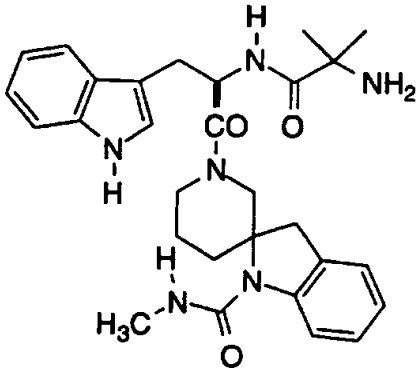


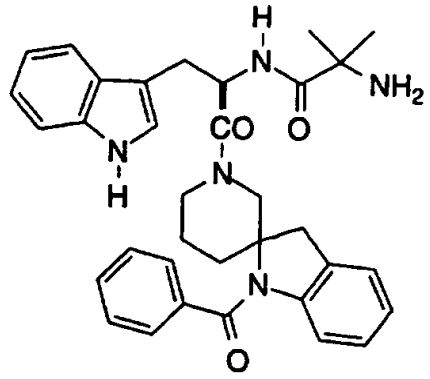


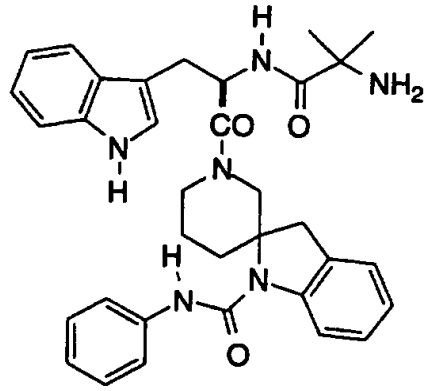


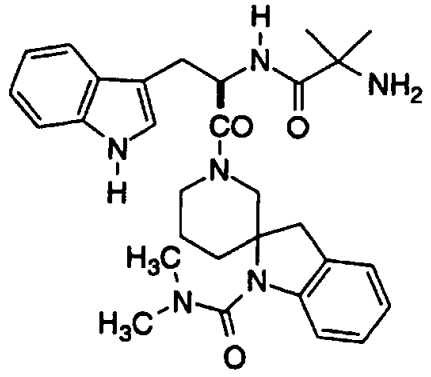


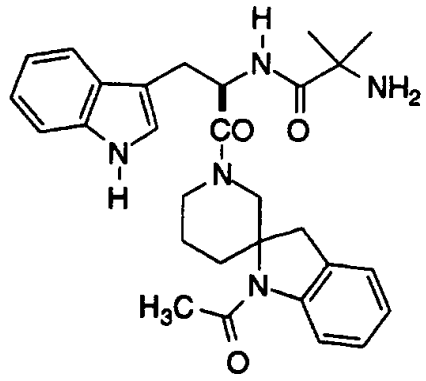


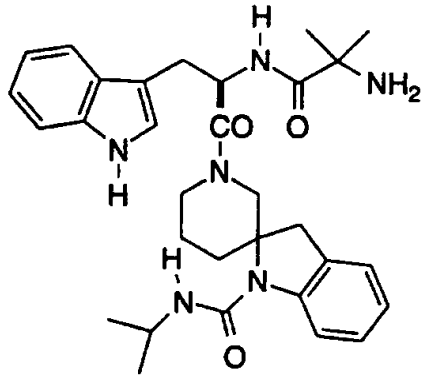


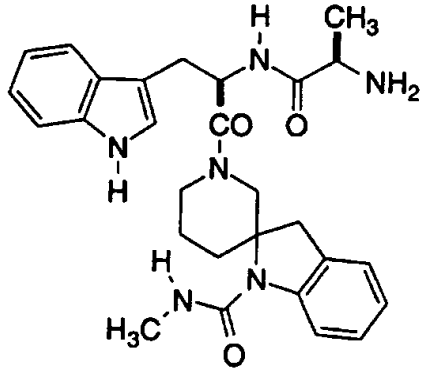


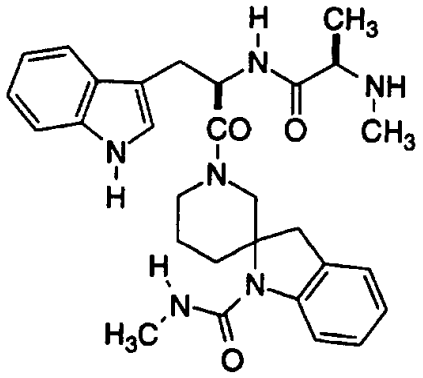


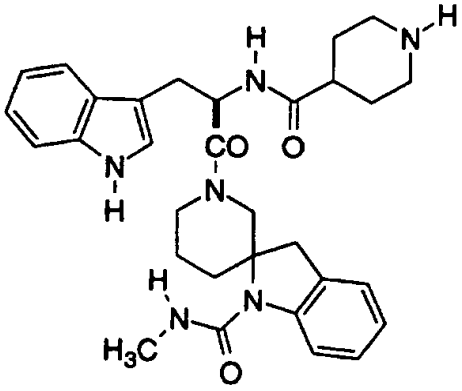


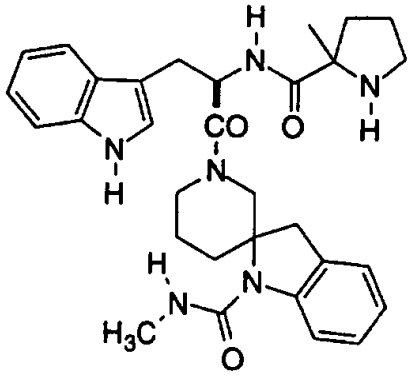


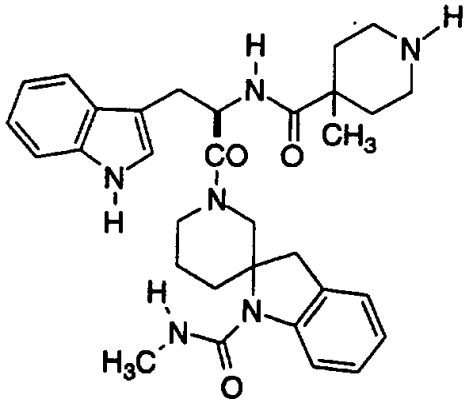


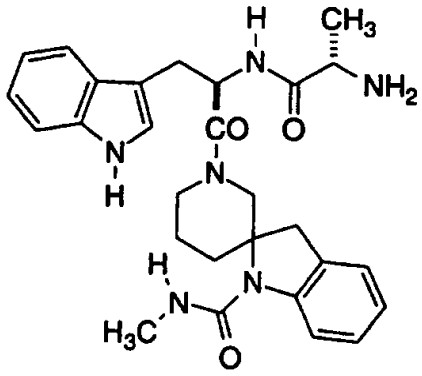


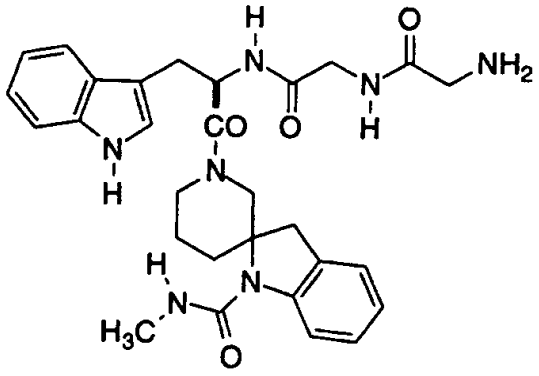


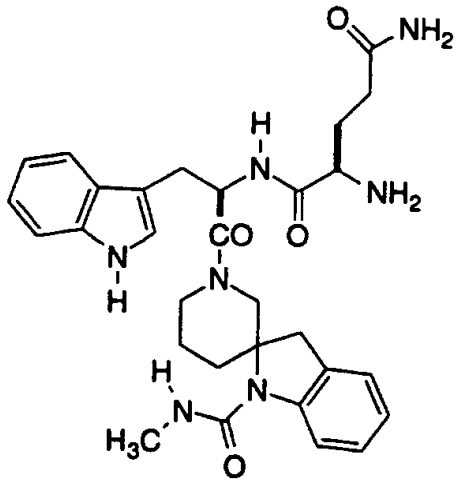


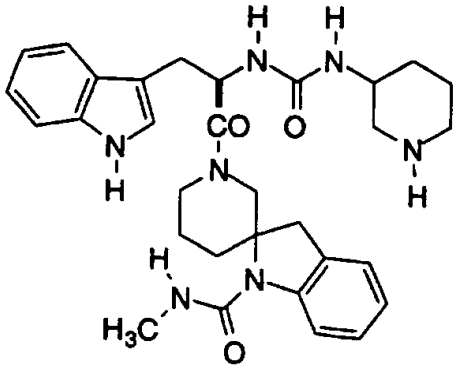


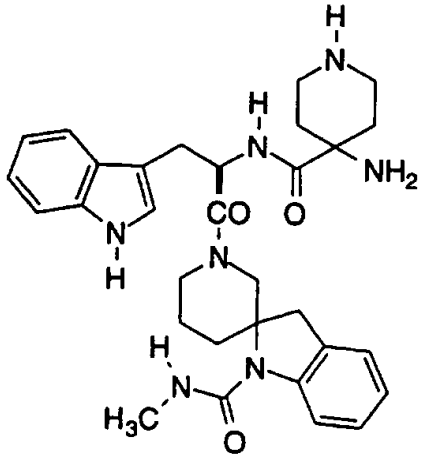


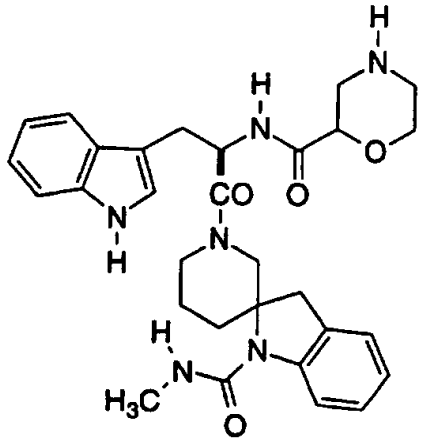


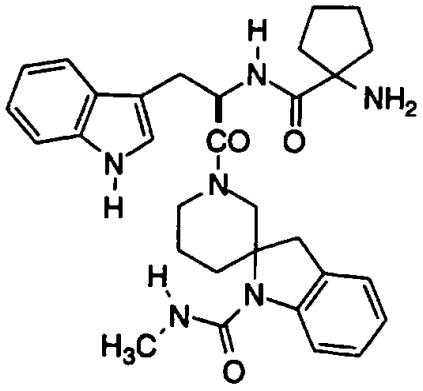


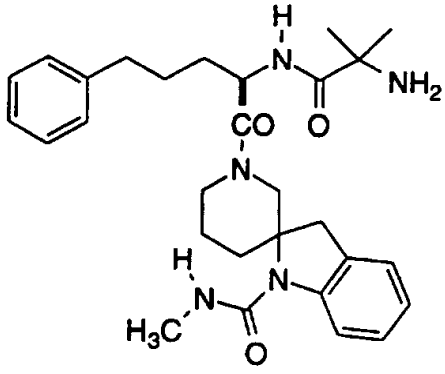


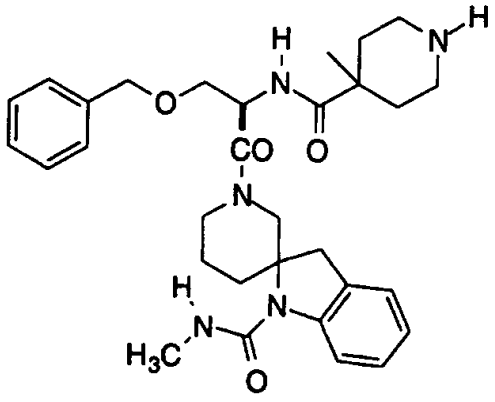


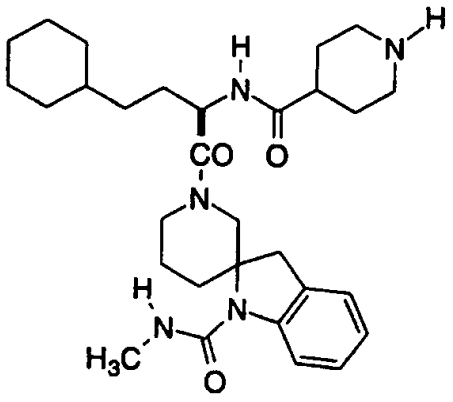


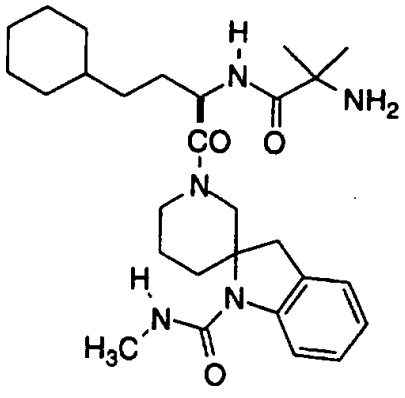


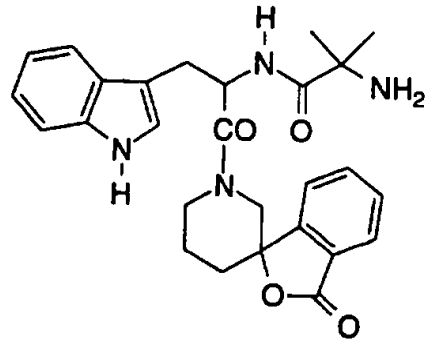


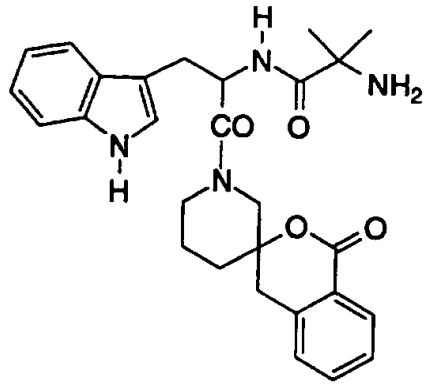


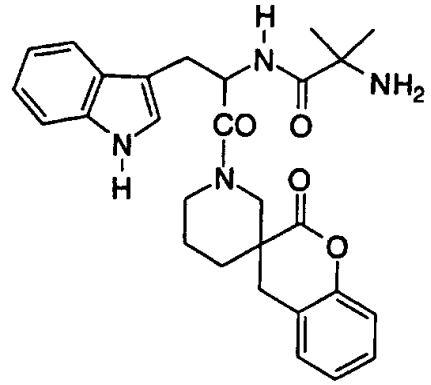


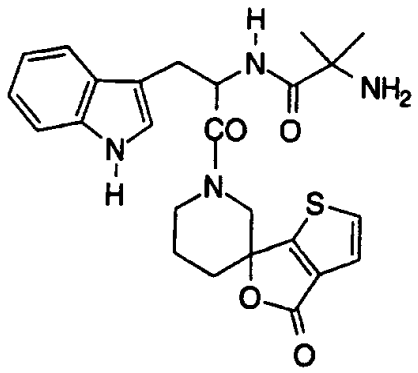


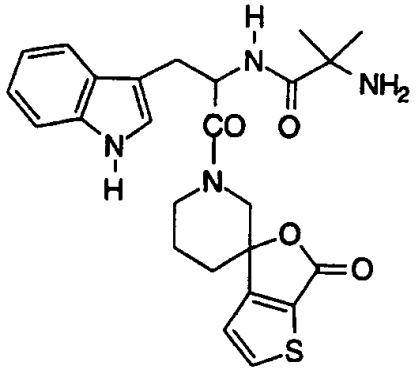


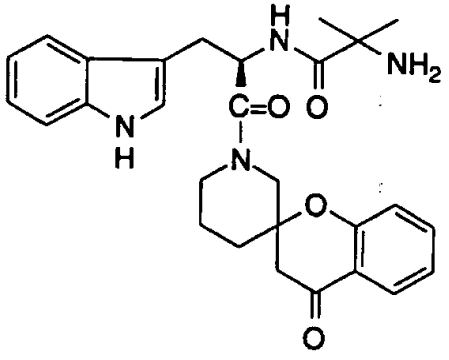


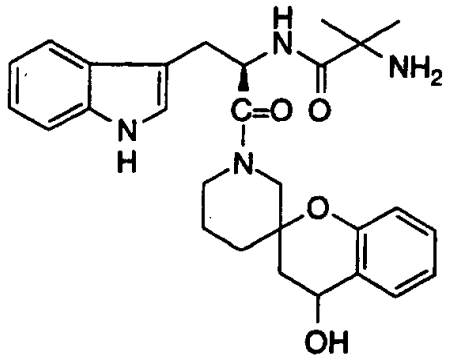


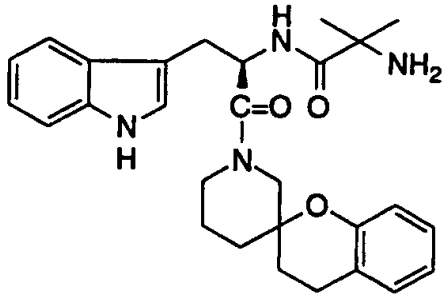


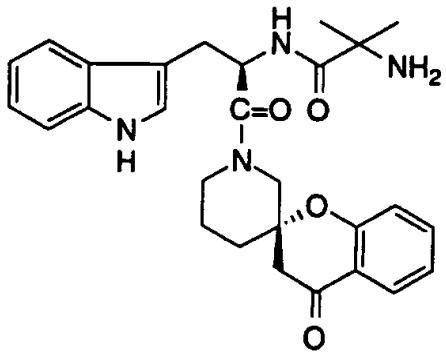


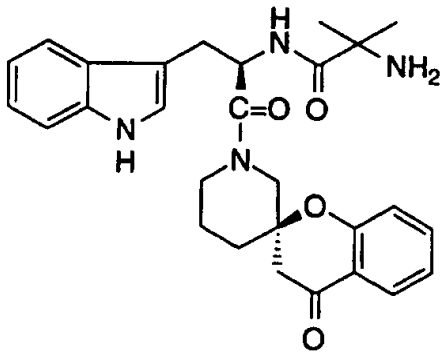


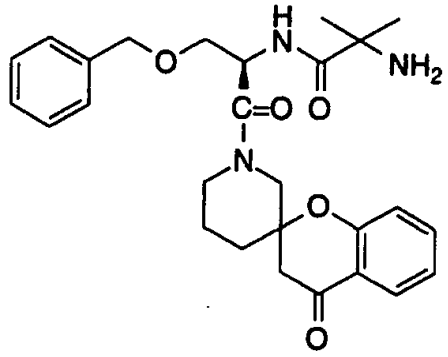


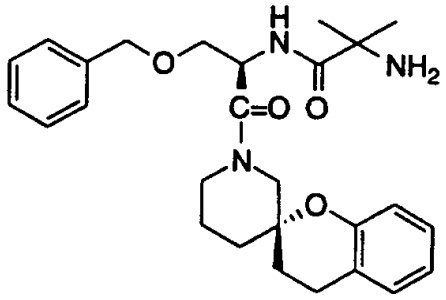


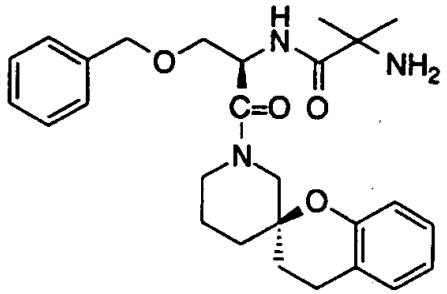


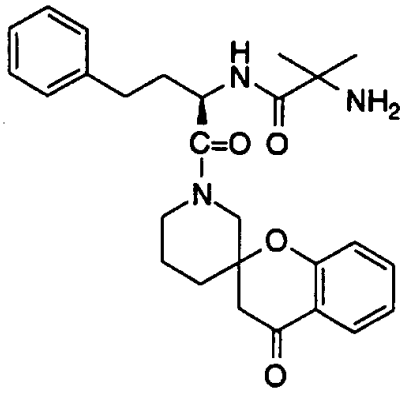


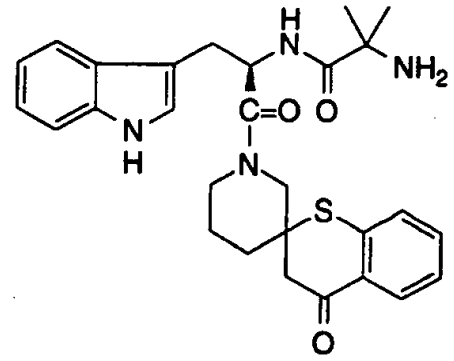


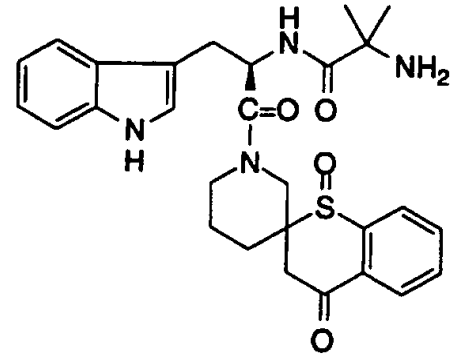


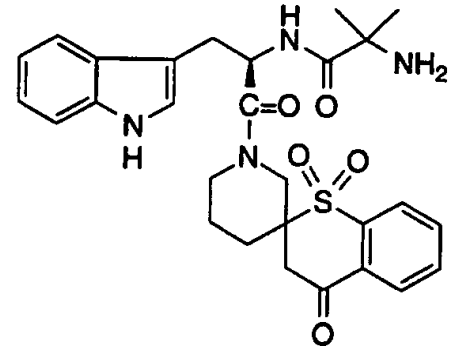












and pharmaceutically acceptable salts and individual diasteromers thereof.

8. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

9. A pharmaceutical composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and a compound of Claim 1.

10. The pharmaceutical composition of Claim 9 wherein the bisphosphonate compound is alendronate.

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

12. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of a compound of Claim 1.

13. A method for the treatment of a disease or a condition which is benefited by the anabolic effects of enhanced growth hormone levels that comprises administering to a patient in need thereof an effective amount a compound of Claim 1.

14. The method of Claim 13 wherein the disease or condition is selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and the treatment of patients recovering from major surgery, wounds or burns.

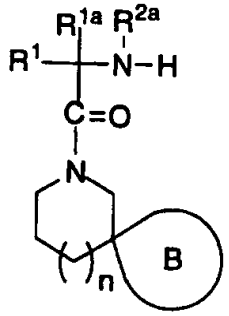
15. A method for increasing the endogenous production or release of growth hormone in a human or an animal which comprises administering to a patient a compound of Claim 1 in combination with an additional growth hormone secretagogue.

16. The method of Claim 15 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

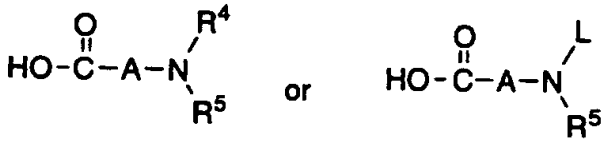
17. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and a compound of Claim 1.

18. The method of Claim 17 wherein the bisphosphonate compound is alendronate.

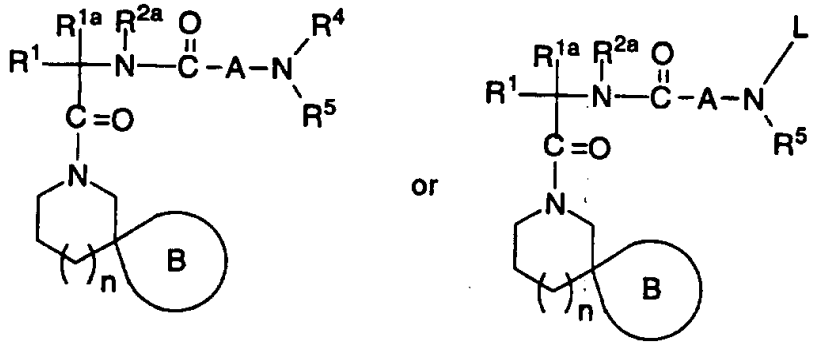
19. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:



with a compound of the formula:



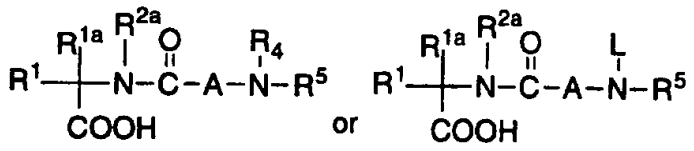
to give a compound of the formula:



;

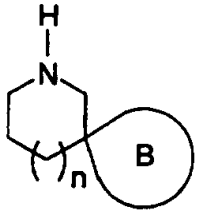
wherein R1, R1a, R2a, R4, R5, A, and B are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

20. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:

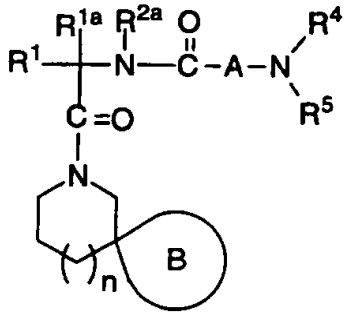


or

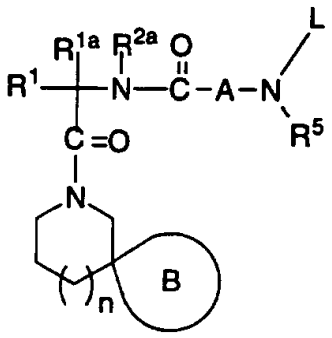
with a compound of the formula:



to give a compound of the formula:



or



;

wherein R1, R1a, R2a, R4, R5, A, and B are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15518

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/445; C07D 487/20
US CL :514/278; 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/17; 514/278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,125,580 A (JANSSEN) 17 March 1964 (17.03.64), see column 1, lines 11-46.	1-20
A, P	US 5,536,716 A (CHEN ET AL.) 16 July 1996 (16.07.96), see entire document, especially columns 1-4.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
07 NOVEMBER 1996

Date of mailing of the international search report
24 DEC 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

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R.W. RAMSUER aco
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-20 (in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15518

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R1, R1a, R2a, R2, R4, R5, R6, R7, B, W, X, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Therefore, the first discernable invention as found in Example A1, the process of making same and the method of increasing levels of endogenous growth hormone in a human using the compound of Example A1, has been searched.